Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/AU04/001830

International filing date: 24 December 2004 (24.12.2004)

Document type: Certified copy of priority document

Document details: Country/Office: AU
Number: 2003907196
Filing date: 24 December 2003 (24.12.2003)

Date of receipt at the International Bureau: 25 January 2005 (25.01.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

PCT/AU2004/001830

Australian Government

Patent Office
Canberra

I, LEANNE MYNOTT, MANAGER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003907196 for a patent by BIOTA SCIENTIFIC MANAGEMENT PTY LTD as filed on 24 December 2003.

WITNESS my hand this
Eighteenth day of January 2005

LEANNE MYNOTT
MANAGER EXAMINATION SUPPORT
AND SALES

Regulation 3.2

Biota Scientific Management Pty Ltd

AUSTRALIA

Patents Act 1990

PROVISIONAL SPECIFICATION

for the invention entitled:

"Polycyclic agents for the treatment of respiratory syncytial virus infections"

The invention is described in the following statement:

POLYCYCLIC AGENTS FOR THE TREATMENT OF RESPIRATORY SYNCYTIAL VIRUS INFECTIONS

Field of the invention

The present invention relates to antiviral compounds, methods for their preparation and compositions containing them, and use at the compounds and composition in the treatment of viral infections. In particular, the invention relates to imidazo-[2,1-a]-isoindole derivatives for the treatment of respiratory syncytial virus infection.

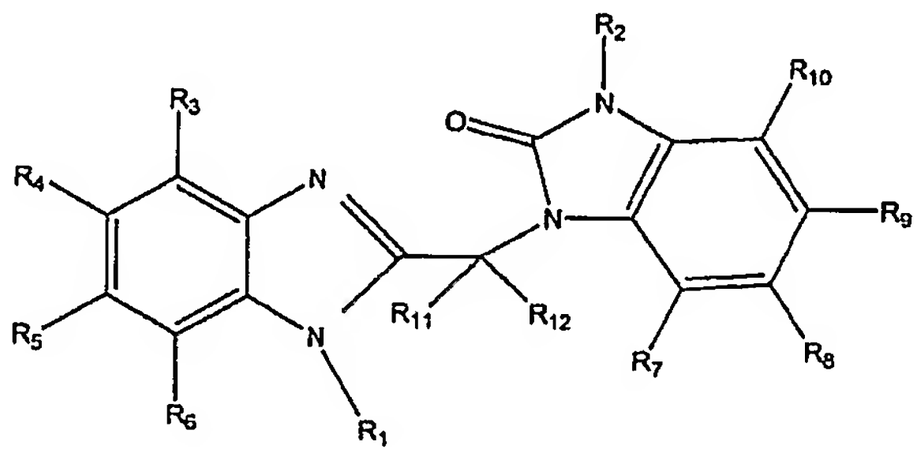
Background Art

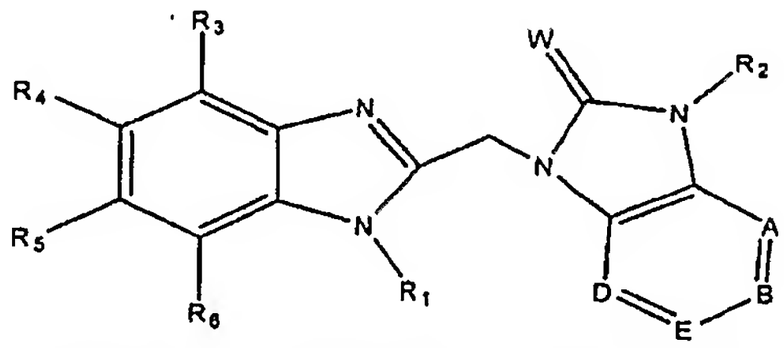
Respiratory syncytial virus (RSV) is the leading cause of lower respiratory tract infection in adults and in young children. In the western world approximately all children have been infected by the age of two. In most cases the RSV infections will only cause minor upper respiratory illness with symptoms resembling that of the common cold. However, severe infection with the virus may result in bronchiolitis or pneumonia which may result in hospitalization or death. Infants who have been born prematurely or have a pre-existing lung disease are a high risk of severe infection and complications.

The only drug currently approved for the treatment of severe RSV is the antiviral medication, Virazole, also known as Ribavirin. This agent has a broad spectrum antiviral with virustatic effects, and acts by inhibiting RSV replication. It also improves arterial blood oxygenation. Unfortunately, the agent is toxic so that administration of the agent is confined to a hospital setting. Its administration is further complicated by the need to follow a strict procedural process when administering the agent in order to minimise the likelihood of certain adverse affects. The agent has a number of adverse effects including sudden deterioration of respiratory function (bronchiospasm). The efficacy of the agent has remained controversial and thus there is a real need to find an alternative agent for the treatment of RSV infection.

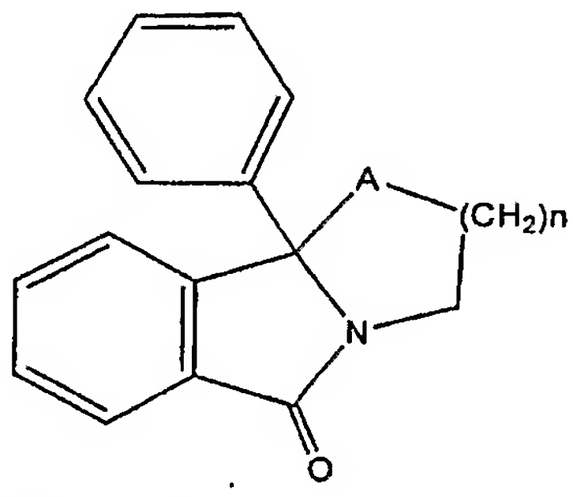
A number of agents are known to inhibit RSV. Published patent applications WO 01/95910 and WO 02/26228 (Bristol Myers Squib Company), the contents of which are incorporated by cross reference, describe a number of different types of compounds which exhibit anti-RSV activity in their description of the background art. Moreover,

these applications describe compounds having antiviral activity against RSV of the formula



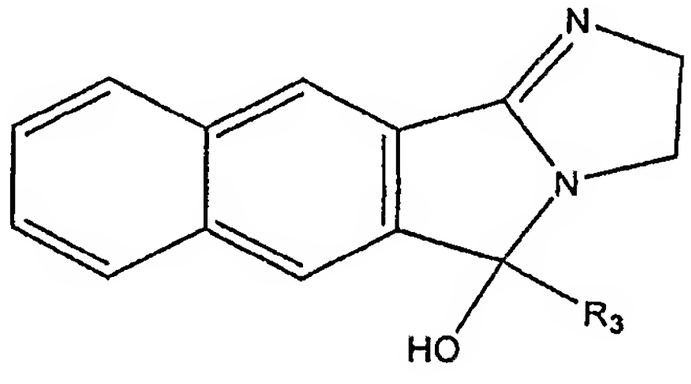


There are also a number of patent specifications that disclose imidazo-[2,1-a]-isoindole derivatives for uses other than treating RSV. US Patent 3,507,863 describes a number of polycyclic compounds that have anti-inflammatory and anti-convulsive activity. These compounds have the following general structure



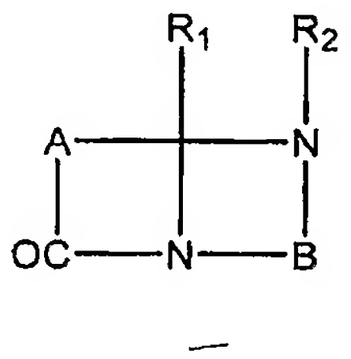
where A is –NH-, -O- or –S-, and n is 1-3.

US Patent 3,770,766 describes polycyclic compounds that have antidepressant activity, and have the following general structure

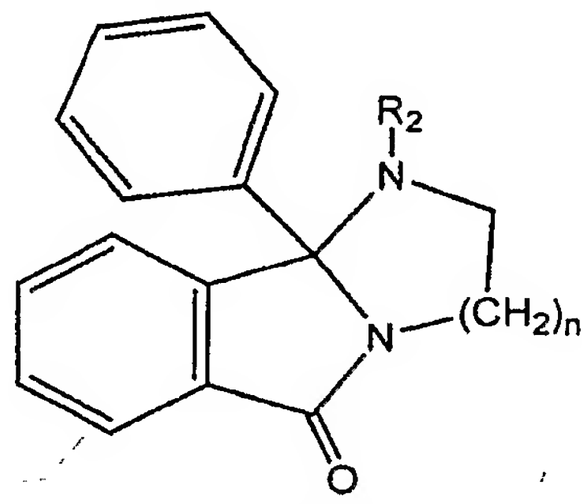


where R_3 is selected from various aromatic substituents.

US Patent 4,058,529 discloses anti-inflammatory and anti-convulsive activity polycyclic compounds of the general formula A, and includes compounds of the formula B where R_2 is hydrogen or substituted lower alkyl and aralkyl groups and n is 1-3.

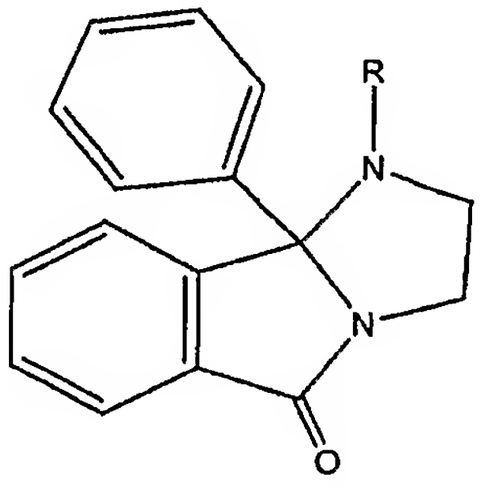


Formula A



Formula B

Canadian patent application 2,108,899 discloses various oxazolo-[2,3-a]-isoindole and imidazo-[2,1-a]-isoindole derivatives for use in antiviral medicaments, particularly for treating diseases caused by retroviruses such as HIV. The specification generally describes compounds of the structure below where R is C_1-C_6 alkyl group or C_1-C_6 acyl group, and specifically discloses compounds where R is $-COCH_3$ or $-CH_3$.

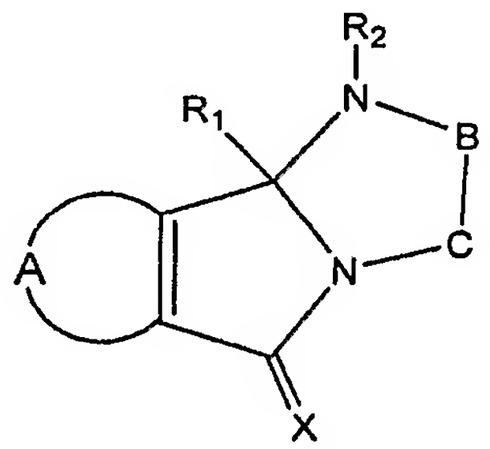


This application teaches that compounds of the general formula shown inhibit DNA and RNA viruses by inhibition of the action of viral reverse transcriptase.

Summary of the Invention

The invention relates to the discovery that certain compounds exhibit favourable anti-RSV activity by inhibition of the RSV virus's essential fusion processes.

This invention provides for the use of a compound of formula I



Formula I

its salts, and pharmaceutically acceptable derivatives thereof, in the treatment of respiratory syncytial virus (RSV) infections, wherein

R_1 is C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, $-(CH_2)_nC_{3-7}$ cycloalkyl, $-(CH_2)_nC_{4-7}$ cycloalkenyl, $-(CH_2)_n$ aryl, $-(CH_2)_n$ arylC_{1-12} alkyl, $-(CH_2)_n$ arylC_{2-12} alkenyl, $-(CH_2)_n$ arylC_{2-12} alkynyl, and $-(CH_2)_n$ heterocyclyl, where n is 0-6 and said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl and heterocyclyl groups are optionally substituted;

R_2 is hydrogen, $-CH_2R_3$, $-C(Y)R_3$, $-C(Y)N(R_4)R_3$, $-S(O)_wR_5$, where R_3 is selected from hydrogen, C_{1-12} alkyl, C_{2-12} alkenyl, C_{2-12} alkynyl, $-(CH_2)_mC_{3-7}$ cycloalkyl, $-(CH_2)_mC_{4-7}$ cycloalkenyl, $-(CH_2)_m$ aryl, $-(CH_2)_m$ arylC_{1-12} alkyl, $-(CH_2)_m$ arylC_{2-12} alkenyl, $-(CH_2)_m$ arylC_{2-12} alkynyl, $-(CH_2)_m$ heterocyclyl, $-S-R_5$ and $-O-R_5$; m is 0-6; R_4 is hydrogen or is C_{1-6} alkyl; R_5 is C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, benzyl, aryl and heterocyclyl; and w is 0, 1 or 2, and said alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl and heterocyclyl groups are optionally substituted;

X and Y are independently selected from O, S and NR_6, where R_6 is independently selected from hydrogen, lower alkyl, hydroxy and lower alkoxy;

A together with the atoms to which it is attached, forms an optionally substituted aromatic ring;

B-C together with the atoms to which they are attached, forms an optionally substituted heterocyclic ring having from 5 to 8 ring atoms.

The invention also provides for the use of compounds of formula I, its salts, and pharmaceutically acceptable derivatives thereof, in the treatment of RSV infections by the inhibition of the viruses fusion processes.

The invention also provides novel compounds of formula I, their salts, and pharmaceutically acceptable derivatives thereof.

Description of Preferred Embodiments

As used herein the term "aromatic" refers to aryl rings or ring systems and aromatic heterocyclic rings or ring systems, as known as heteroaryl or heteroaromatic.

As used herein the term "aryl" refers to carbocyclic (non-heterocyclic) aromatic rings or ring systems. The aromatic rings may be mono- or bi-cyclic ring systems. The aromatic rings or ring systems are generally composed of 5 to 10 carbon atoms. Examples of suitable aryl groups include but are not limited to phenyl, biphenyl, naphthyl, tetrahydronaphthyl, and the like.

Preferred aryl groups include phenyl, naphthyl, indenyl, azulenyl, fluorenyl or anthracenyl.

The term "heterocyclic" or "heterocyclyl" as used herein refers to mono or bicyclic rings or ring systems that include one or more heteroatoms selected from N, S and O. The rings or ring systems generally include 1 to 9 carbon atoms in addition to the heteroatom(s) and may be saturated, unsaturated, aromatic or pseudoaromatic. The term "pseudoaromatic" refers to a ring system which is not strictly aromatic, but which is stabilized by means of delocalization of electrons and behaves in a similar manner to aromatic rings.

Examples of 5-membered monocyclic heterocycles include furyl, thienyl, pyrrolyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrazolyl, imidazolyl, triazolyl, tetrazolyl, oxadiazolyl, thiadiazolyl and examples of 6-membered monocyclic heterocycles include pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl and triazinyl. The heterocycles may be optionally substituted with a broad range of substituents, and preferably with C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-6} alkynyl, C_{3-6} alkynyl, halo, hydroxy, mercapto, trifluoromethyl, amino, cyano or mono or di(C_{1-6}alkyl) amino.

The heterocycle may be fused to a carbocyclic ring such as phenyl, naphthyl, indenyl, azulenyl, fluorenyl, and anthracenyl.

Examples of 9 and 10-membered bicyclic heterocycles include indolyl, benzofuranyl, benzothienyl, benzoxazolyl, benzothiazolyl, benzisoxazolyl, benzisothiazolyl, indazolyl, isoquinolinyl, quinolinyl, quinoxalinyl, cinnolinyl, phthalazinyl, quinazolinyl, benzotriazinyl and the like.

Examples of preferred heterocyclic radicals include (optionally substituted) isoxazoles, isothiazoles, 1,3,4-oxadiazoles, 1,3,4-thiadiazoles, 1,2,4-oxadiazoles, 1,2,4-thiadiazoles, oxazoles, thiazoles, pyridines, pyridazines, pyrimidines, pyrazines, 1,2,4-triazines, 1,3,5-triazines, benzoxazoles, benzothiazoles, benzisoxazoles, benzisothiazoles, quinolines and quinoxalines.

Examples of unsaturated 5-membered heterocyclic rings include oxazole, thiazole, imidazole, 1,2,3-triazole, isoxazole, isothiazole, pyrazole, furan, thiophene and pyrrole.

Examples of unsaturated 6-membered heterocyclic rings include pyridine, pyrimidine, pyrazine, pyridazine and 1,2,4-triazine.

In a preferred embodiment, the heterocyclic ring is an aromatic ring selected from the group consisting of furyl, thienyl, pyridyl, pyrrolyl, oxazolyl, thiazolyl, imidazolyl, pyrazolyl, isoxazolyl, isothiazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,4-oxadiazol-5-one, 1,2,3-triazolyl, 1,3,4-thiadiazolyl, pyridazinyl, pyrimidinyl, pyrazinyl, 1,3,5-triazinyl, indolizinyl, indolyl, isoindolyl, 3H-indolyl, indolinyl, benzo[b]furanyl, benzo[b]thiophenyl, 1H-indazolyl, benzimidazolyl, tetrazole, uridinyl, and cytosinyl.

More preferably the heterocyclic ring is an aromatic ring selected from isoxazolyl, oxazolyl, imidazolyl, thiazolyl, isothiazolyl, pyridyl, pyrimidinyl, furyl, pyrazolyl, pyridazinyl, furazanyl and thienyl.

In another preferred embodiment, the heterocyclic ring is a non-aromatic ring selected from the group consisting of pyrrolidine, imidazoline, 2-imidazolidone, 2-pyrrolidone, pyrrolin-2-one, tetrahydrofuran, 1,3-dioxolane, piperidine, tetrahydropyran, oxazoline, 1,3-dioxane, 1,4-piperazine, morpholine and thiomorpholine.

Unless otherwise defined, the term "optionally substituted" as used herein means that a group may include one or more substituents that do not interfere with the binding activity of the compound of formula I. In some instances the substituent may be selected to improve binding. The group may be substituted with one or more substituents selected from halogens, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, $-(CH_2)_pC_{3-7}$ cycloalkyl, $-(CH_2)_pC_{4-7}$ cycloalkenyl, $-(CH_2)_p$ aryl, $-(CH_2)_p$ heterocyclyl, $-C_6H_4S(O)_tC_{1-6}$ alkyl, $-C(Ph)_3$, $-(CH_2)_pZ$, –COZ, -CN, -OR, -OCOR, -COR, -COOR, -OCONR'R", –NR'R", -NRCOR', -NRCONR'R", -NRC(S)NR'R", $-NRSO_2R'$, –NRCOOR', -C(NR)NR'R", -CRNOR', -C(=NOH)NR'R", -CONR'R", -C(=NCN)-NR'R", -C(=NR)NR'R", –C(=NR')SR", -NR'C(=NCN)SR", $-CONRSO_2R'$, –C(S)NR'R", $-S(O)_tR$, $-SO_2NR'R"$, $-SO_2NRCOR'$, $-OS(O)_2R$, $-PO(OR)_2$ and $-NO_2$; where p is 0-6, t is 0-2, Z is an N-linked amino acid selected from the group consisting of alanine, asparagine, aspartic acid, glutamic acid, glutamine, glycine, pipecolic acid, α-amino-butyric acid, α-amino-propanoic acid, and iminodiacetic acid, Z being linked through a nitrogen atom of said N-linked amino acid to the carbon atom, and each R, R' and R" is independently selected from H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-7} cycloalkyl, C_{4-7} cycloalkenyl, aryl, heterocyclyl, C_{1-6} alkylaryl, C_{1-6} alkylheterocyclyl, wherein the alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, benzyl, aryl and heterocyclyl may be optionally substituted with one to six of same or different selected from halogen, hydroxy, lower alkoxy, $-CO_2H$, and $-NO_2$; or when R' and R" are attached to the same nitrogen atom, they may, together with the atom to which they are attached, form a 5 to 7 membered nitrogen containing heterocyclic ring.

When the optional substituent is or contains an alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, aryl or heterocyclyl group, the group may itself be optionally substituted with one to six of the same or different halogen atoms or hydroxy or $-NO_2$.

In relation to non-aromatic carbocyclic or heterocyclic compounds, unless otherwise defined such compounds may also be optionally substituted optionally substituted with one or two =O groups, instead of or in addition to the above described optional substituents.

Examples of optional substituents include halogens, C_{1-4} alkyl, C_{2-4} alkenyl, C_{2-4} alkynyl, C_{1-4} alkoxy, C_{1-4} haloalkyl, $-CF_3$, -OH, phenyl, $-NH_2$, $-NHC_{1-4}$ alkyl, $-N(C_{1-4})_2$, -CN, mercapto, C_{1-4} alkylcarbonyl and C_{1-4} alkoxycarbonyl.

As used herein the term "C_{1-12} alkyl" refers to straight chain or branched saturated hydrocarbon group having from 1 to 12 carbon atoms. Examples of such alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butylisobutyl, sec-butyl or tert-butyl. Similarly "C_{1-6} alkyl" or "lower alkyl" refers to such groups having from 1 to 6 carbon atoms.

As used herein the term "C_{3-7} cycloalkyl" refers to non-aromatic, saturated cyclic groups having from 3 to 7 carbon atoms. Examples include cyclopentyl and cyclohexyl.

As used herein the term "alkoxy" refers to a straight or branched alkyl group covalently bound via an O linkage and the terms "C_{1-6} alkoxy" and "lower alkoxy" refer to such groups containing from one to six carbon atoms, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy and the like.

As used herein the term "C_{2-12} alkenyl" refers to groups formed from C_{2-12} straight chain or branched non-cyclic hydrocarbon containing one or more double bonds. Examples of C_{2-12} alkenyl include allyl, 1-methylvinyl, butenyl, iso-butenyl, 1, 3-butadienyl, 3-methyl-2-butenyl, 1,3-butadienyl, 1,4-pentadienyl, 1-pentenyl, 1-hexenyl, 3-hexenyl, 1,3-hexadienyl, 1,4-hexadienyl and 1, 3, 5-hexatrienyl.

As used herein the term "C_{4-7} cycloalkenyl" refers to non aromatic cyclic carbocycles having 4 to 7 carbon atoms and having one or more double carbon bonds. Examples include cyclopentenyl, 1-methyl-cyclopentenyl, cyclohexenyl, 1,3-cyclopentadienyl, 1,3-cyclohexadienyl and 1,4-cyclohexadienyl.

As used herein the term "C_{2-12} alkynyl" refers to C_{2-12} straight or branched non-cyclic hydrocarbon containing one or more triple bonds, preferably one or two triple bonds. Examples include 2-propynyl and 2- or 3-butynyl.

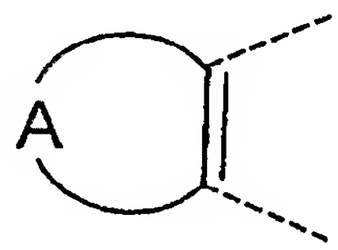
The term "aryl C_{1-12} alkyl" refers to carbocyclic aromatic rings or ring systems as previously described and substituted by a C_{1-12} alkyl group, also as previously described. Likewise the terms "aryl C_{2-12} alkenyl" and "aryl C_{2-12} alkynyl" refer to carbocyclic aromatic rings or ring systems as previously described and substituted by a C_{2-12} alkenyl or C_{2-12} alkynyl group, as previously described.

The aryl group and the alkyl, alkenyl or alkynyl group may be optionally substituted. Preferably the aryl group is not optionally substituted.

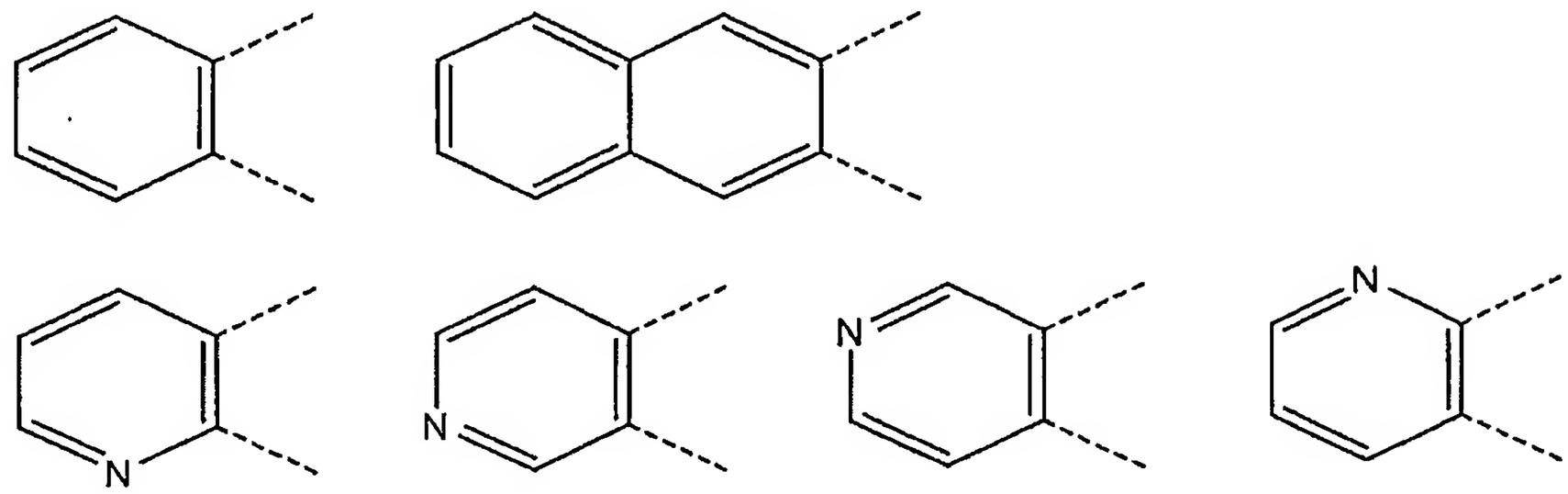
Preferably the alkyl, alkenyl or alkynyl group is optionally substituted, and more preferably with a substituent selected from halogens, -CN, -NR'R", -COR, -COOR, or –CONR'R". Preferably R, R' and R" are independently selected from hydrogen or lower alkyl.

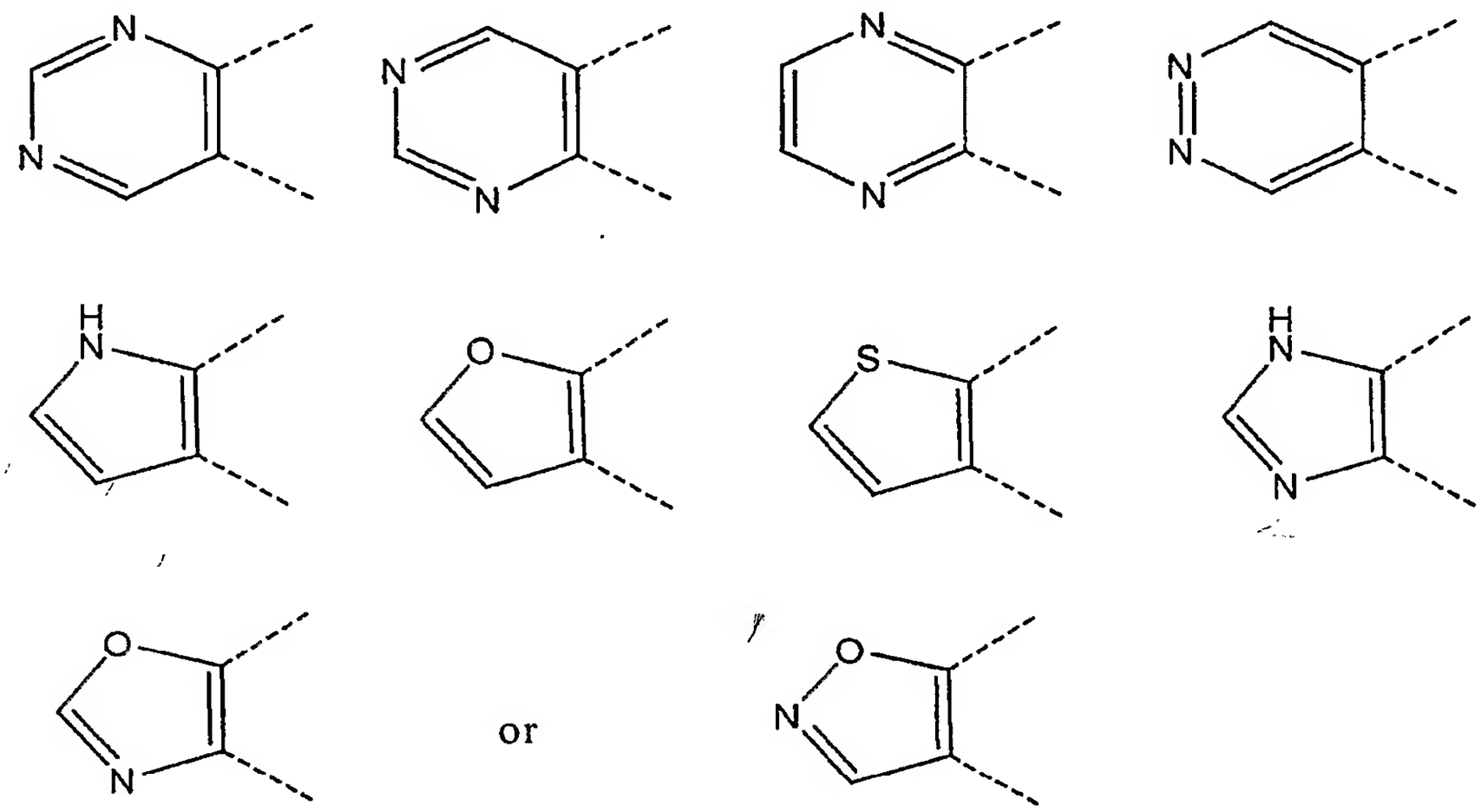
As used herein the term "halo" or "halogen" refers to fluoro, chloro, bromo and iodo groups.

Particularly preferred compounds of the invention include those compounds where A is a bivalent link of 3 or 4 atoms selected from C, N, O and S. In that arrangement A and the atoms to which they are attached together form an aromatic ring having five or six ring atoms. When the linking atoms are all carbon, the ring formed is a carbocyclic aromatic ring or ring system. When the linking atoms include one or more of N, O or S then the ring formed is an aromatic heterocyclic ring. Examples include where the substructure



is:-



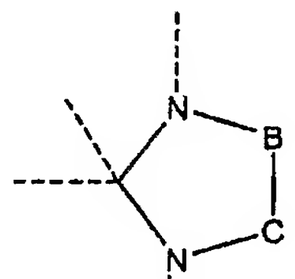


or

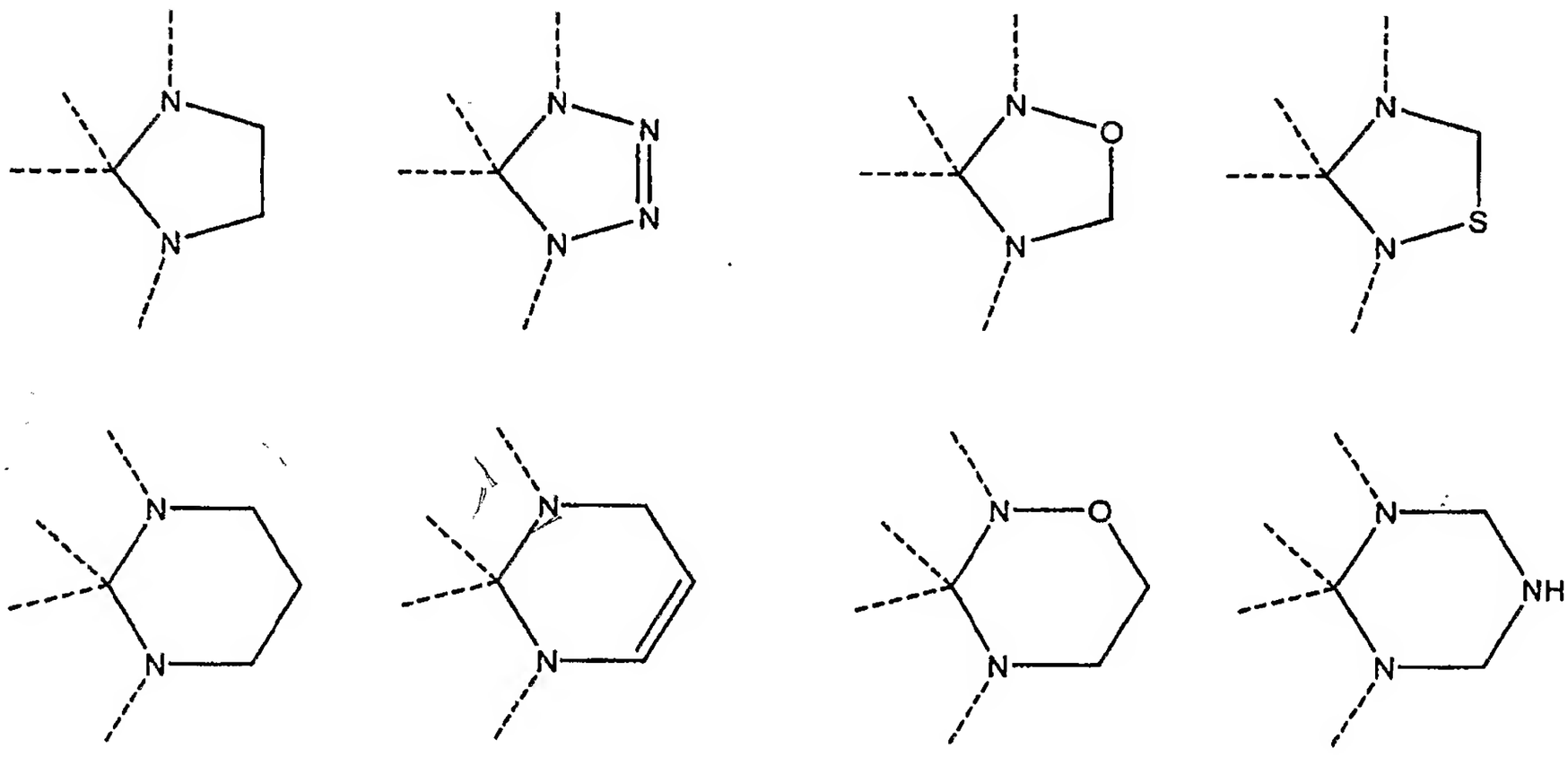
The aromatic rings may be optionally substituted, preferably by no more than 3 substituents. Of the optional substituents, it is particular preferred to use 1 to 3 substituents selected from halo, lower alkyl, hydroxy, lower alkoxy, amino, loweralkylamino, carboxy, carboxamido, phenyl and benzyl.

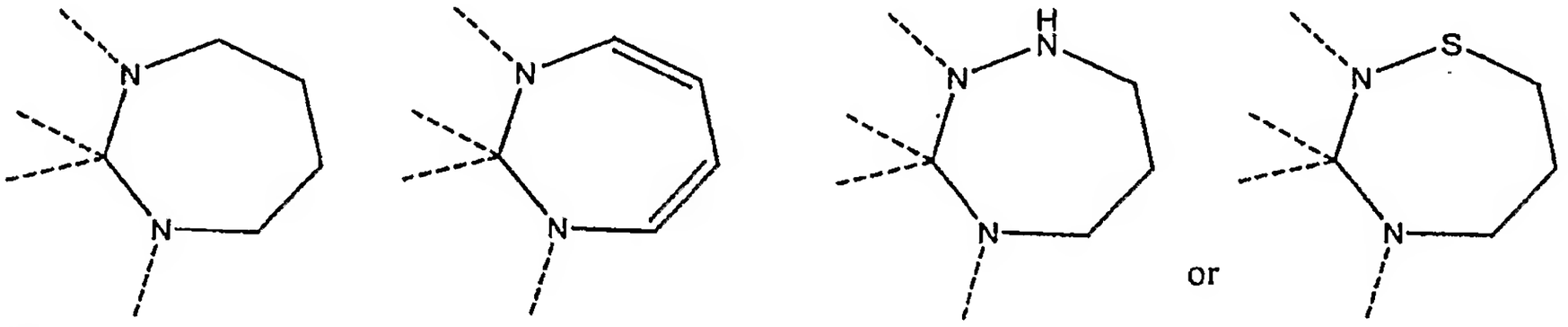
In respect of the heterocyclic ring formed by B-C, it will be understood that this ring can not be selected from all of the heterocyclic rings discussed earlier in relation to the meaning of the term due to the atoms to which B-C are attached. This ring is limited to monocyclic, non-aromatic heterocyclic rings that include at least two nitrogen atoms. The ring may include additional hetero atoms and may be partially unsaturated.

Particularly preferred are compounds in which B-C represents a bivalent link of 1 to 3 atoms. The link B-C together with the atoms to which it is attached forms a non-aromatic heterocyclic ring. Examples include where the substructure:-



is:





or

In a preferred form of the invention, B-C represents $-CH_2-(CH_2)_z-$, where z is 1-4.

The atoms forming the link B-C may be optionally substituted, preferably by no more than 3 substituents. A broad range of substituents are possible and include halo, lower alkyl, hydroxy, lower alkoxy, phenyl and benzyl.

A preferred form of the invention includes those compounds where B-C represents -CH_2CH_2-.

Preferably X is oxygen or sulphur, more preferably X is oxygen.

Preferably fused ring A is a fused phenyl or pyridyl ring.

In an embodiment of the invention fused ring A and the ring containing the bivalent link B-C are optionally substituted with one or two substituents independently selected from halogen and C_{1-6} alkyl. Preferably fused ring A and the ring containing the bivalent link B-C are not substituted.

Preferably R_1 is optionally substituted phenyl or alkyl. The phenyl ring is preferably substituted with lower alkyl, alkoxy or halo. Most preferably R_1 is 4-chlorophenyl-.

R_1 alternatively is -phenylC_{1-10} alkyl, where the alkyl is substituted with halo, –CN, -NR'R", -CO_2R or –CONR'R", where R, R' and R" are independently selected from hydrogen or lower alkyl. More preferably the alkyl chain is in the 4-position of the phenyl ring, and substituents are attached to the carbon at the free end of the alkyl group.

When R_2 is –CH_2-R_3, it is preferred that R_3 is –$(CH_2)_m$ aryl or –$(CH_2)_m$ heteroaryl, where m is 0 to 3. It is particularly preferred for R_3 to be benzyl (m=1). The ring atoms may by optionally substituted with a broad range of substituents. Preferred substituents are selected from halo, lower alkyl, hydroxy, lower alkoxy and phenyl.

When R_2 is –C(Y)-R_3, it is preferred that Y is O. It is also preferred that R_3 is –$(CH_2)_m$ aryl or –$(CH_2)_m$ heteroaryl, where m is 0 to 3. It is particularly preferred for R_3 to be phenyl (m=0). The aryl or heteroaryl ring atoms may be optionally substituted with a broad range of substituents. Preferred substituents include halo, lower alkyl, hydroxy, lower alkoxy and phenyl.

When R_2 is –COR_3, it is also preferred for R_3 to be -phenylC_{1-10} alkyl, where the alkyl is substituted with halo, –CN, -NR'R", -CO_2R or –CONR'R", where R, R' and R" are independently selected from hydrogen or lower alkyl. More preferably the alkyl chain is

in the 4-position of the phenyl ring, and substituents are attached to the carbon at the free end of the alkyl group.

When R_2 is $-CON(R_4)R_3$ it is preferred for R_4 to be hydrogen and R_3 to be $-(CH_2)_m$ aryl or $-(CH_2)_m$ heteroaryl. Preferably m is 0 to 2, more preferably 0 to 1. The aryl and heteroaryl ring atoms may be optionally substituted with a broad range of substituents. Preferred substituents include halo, lower alkyl, hydroxy, lower alkoxy and phenyl.

Another preferred embodiment of the invention are those compounds where R_2 is $-COR_3$ and fused ring A contains at least one ring nitrogen atom.

When the invention relates to compounds of formula I per se, it is preferred that when R_1 is optionally substituted phenyl, R_2 is not hydrogen. It is also preferred that when R_1 is unsubstituted phenyl, X is O, A together with the atoms to which it is attached forms an unsubstituted phenyl ring and B-C is $-CH_2CH_2-$, R_2 is not unsubstituted C_{1-6} alkyl or $-C(O)C_{1-6}$ alkyl.

It will be appreciated that compound of formula I and some derivatives thereof may have at least one asymmetric centre, and therefore are capable of existing in more than one stereoisomeric form. The invention extends to each of these forms individually and to mixtures thereof, including racemates. The isomers may be separated conventionally by chromatographic methods or using a resolving agent. Alternatively the individual isomers may be prepared by asymmetric synthesis using chiral intermediates. Where the compound has at least one carbon-carbon double bond, it may occur in Z- and E- forms and all isomeric forms of the compounds being included in the present invention.

The salts of the compound of formula I are preferably pharmaceutically acceptable, but it will be appreciated that non-pharmaceutically acceptable salts also fall within the scope of the present invention, since these are useful as intermediates in the preparation of pharmaceutically acceptable salts.

The term "pharmaceutically acceptable derivatives" includes pharmaceutically acceptable esters, prodrugs, solvates and hydrates, and pharmaceutically acceptable addition salts of the compounds or the derivatives. Pharmaceutically acceptable derivatives may include any pharmaceutically acceptable salt, hydrate or any other compound or prodrug which,

upon administration to a subject, is capable of providing (directly or indirectly) a compound of formula I or an antivirally active metabolite or residue thereof.

The pharmaceutically acceptable salts include acid addition salts, base addition salts, salts of pharmaceutically acceptable esters and the salts of quaternary amines and pyridiniums. The acid addition salts are formed from a compound of the invention and a pharmaceutically acceptable inorganic or organic acid including but not limited to hydrochloric, hydrobromic, sulfuric, phosphoric, methanesulfonic, toluenesulphonic, benzenesulphonic, acetic, propionic, ascorbic, citric, malonic, fumaric, maleic, lactic, salicyclic, sulfamic, or tartartic acids. The counter ion of quarternary amines and pyridiniums include chloride, bromide, iodide, sulfate, phosphate, methansulfonate, citrate, acetate, malonate, fumarate, sulfamate, and tartate. The base addition salts include but are not limited to salts such as sodium, potassium, calcium, lithium, magnesium, ammonium and alkylammonium. Also, basic nitrogen-containing groups may be quaternised with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl and diethyl sulfate; and others. The salts may be made in a known manner, for example by treating the compound with an appropriate acid or base in the presence of a suitable solvent.

The compounds of the invention may be in crystalline form or as solvates (e.g. hydrates) and it is intended that both forms be within the scope of the present invention. The term "solvate" is a complex of variable stoichiometry formed by a solute (in this invention, a compound of the invention) and a solvent. Such solvents should not interfere with the biological activity of the solute. Solvents may be, by way of example, water, ethanol or acetic acid. Methods of solvation are generally known within the art.

The term "pro-drug" is used in its broadest sense and encompasses those derivatives that are converted *in vivo* to the compounds of the invention. Such derivatives would readily occur to those skilled in the art, and include, for example, compounds where a free hydroxy group is converted into an ester derivative or a ring nitrogen atom is converted to an N-oxide. Examples of ester derivatives include alkyl esters, phosphate esters and those formed from amino acids, preferably valine. Any compound that is a prodrug of a compound of the invention is within the scope and spirit of the invention.

The term "pharmaceutically acceptable ester" includes biologically acceptable esters of compound of the invention such as sulphonic, phosphonic and carboxylic acid derivatives.

Thus, in another aspect of the invention, there is provided a prodrug or pharmaceutically acceptable ester of a compound of formula I.

In another aspect of the invention, there is provided a pharmaceutical composition that comprises a therapeutically effective amount of one or more of the aforementioned anti-RSV compounds of formula I, including pharmaceutically derivatives thereof, and optionally a pharmaceutically acceptable carrier or diluent.

In further aspect of the present invention, there is provided the use of a compound of formula I, its salts or pharmaceutically acceptable derivatives thereof in the preparation of a medicament for the therapeutic or prophylactic treatment of RSV infections.

In another aspect of the invention, there is provided a method of treating RSV by the administration of a compound of formula I, including the administration of pharmaceutically acceptable salts, or derivatives such as prodrugs of formula I, or a composition containing at least one compound of formula I.

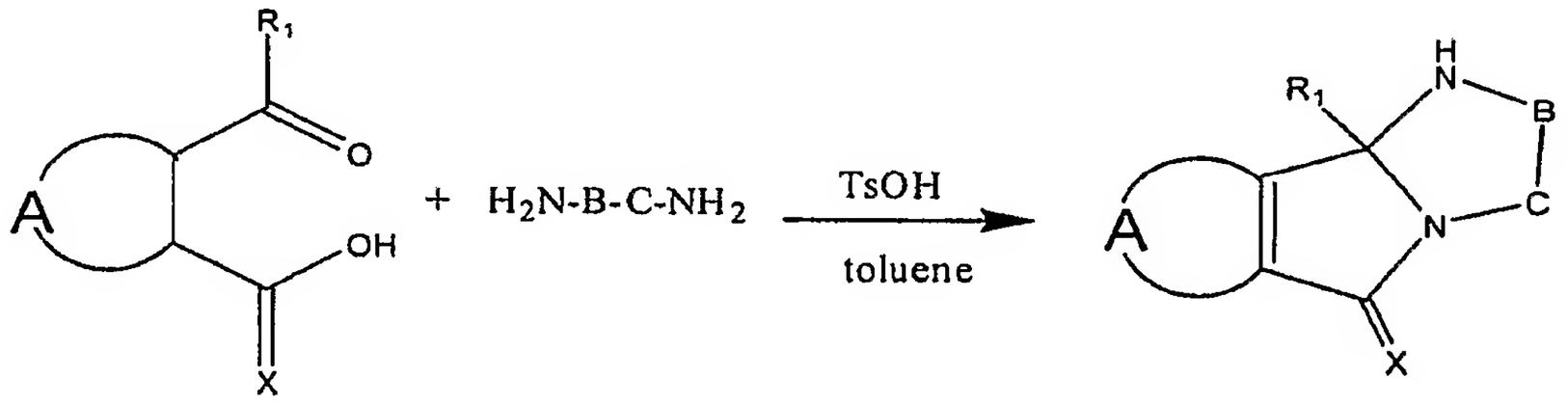
In another aspect of the invention, there is provided a method for treating mammals infected with RSV, and in need thereof, which comprises administering to said mammal a therapeutically effective amount of one or more of the aforementioned compounds of having formula I or pharmaceutically acceptable derivatives thereof.

In another aspect of the invention, there is provided a method for preventing the infection of mammals with RSV, which comprises administering to said mammal a therapeutically effective amount of one or more of the aforementioned compounds of having formula I, or pharmaceutically acceptable derivatives thereof.

In a further form of the invention there is provided a process for the production of compounds of formula I. These compounds may be prepared using the procedure outlined in the following methods.

Scheme 1 depicts a general process for manufacture of a compound of formula I (R_2=H) via Formula II. Formula II may be either purchased commercially or prepared using a modification of the methods described by Yamaguchi, M. *et. al*, *J. Med. Chem.* **1993**, *36*, 4052-4060 or Natsugari, H. *et.*al, *J. Med. Chem.* **1995**, *38*, 3106-3120.

Scheme 1

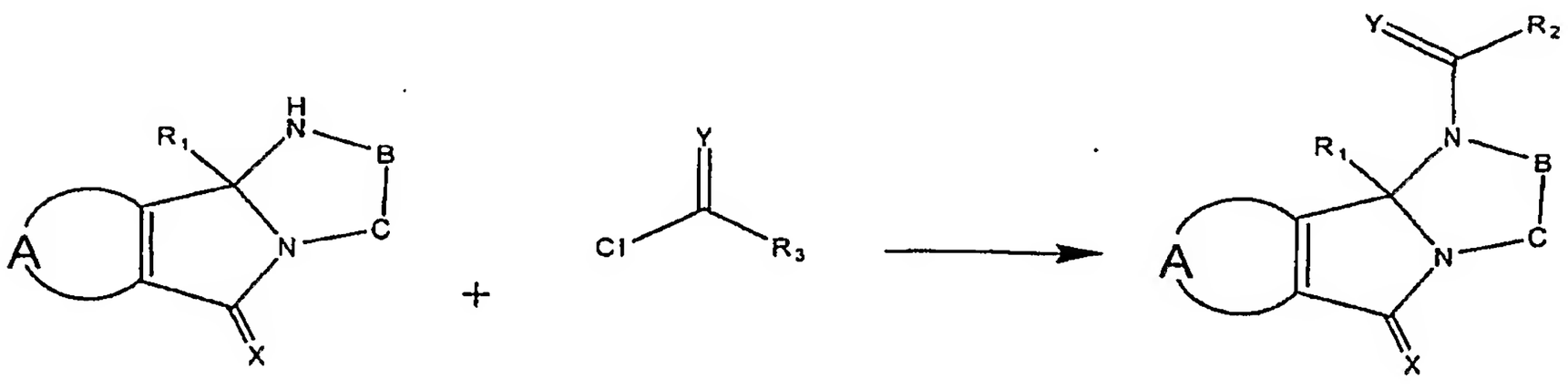


Formula II Formula I

In general, one equivalent of an appropriate 2-(Aroyl)benzoic acid of formula II, is reacted with approximately 3 equivalents of an appropriate diamine of the general formula H_2N-B-C-NH_2. The mixture is heated under reflux in an inert solvent, such as toluene or xylene, with a Dean-Stark apparatus for 3-10 h. A catalyst, such as an acid tosylate, can be used. After this time the reaction is allowed to cool and the product filtered and recrystallised from an appropriate solvent. If no precipitate forms the solvent is evaporated *in-vacuo* and the residue recrystallised or purified using flash chromatography or preparative HPLC.

The selected compounds of formula I can also be produced by the methods described in US 4,058,529, Sulkowski, T.S., *et. al*, *J. Org. Chem.* **1967**, *32*, 2180-2184 and Houlihan, W.J. , *et. al*, *J. Med. Chem.* **1975**, *18*, 182-185. Other (novel) compounds of formula I may be obtained by acylating compounds of Formula I (R_2 is H) as described in Scheme 2.

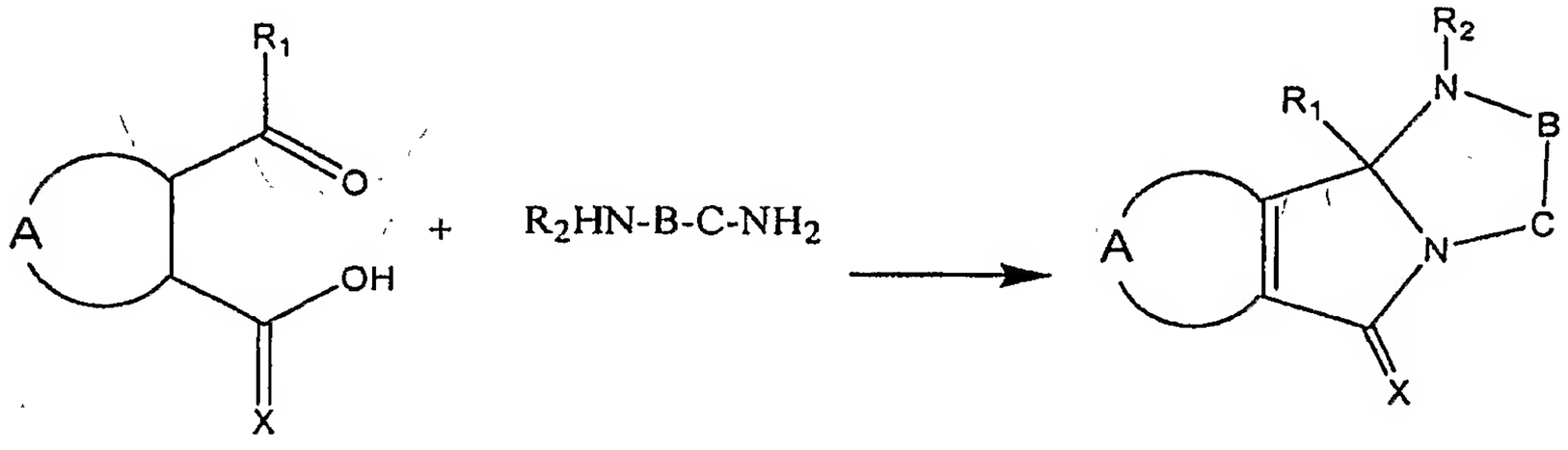
Scheme 2



Formula I (R_2 = H) Formula I

Two equivalents of diisopropylethylamine or triethylamine are added to one equivalent of imidazoisoindolone in THF at 0°C. An acid chloride, or other acylating agent, is added to the mixture and the reaction monitored by HPLC. When the reaction is complete the reaction is quenched with water and the product extracted into a suitable organic solvent and worked up accoding to standard methods. Similar acylation may also be carried out by reacting one equivalent of the appropriate imidazoisoindolone with one equivalent of the appropriate acid chloride in xylene at 120°C for 1-24h. The reaction is then allowed to cool and the product isolated.

N-Alkylated compounds of Formula I are best obtained using suitable mono-N-alkylated diamines. These may be prepared by known methods for example that described by Kruse L.I., *et. al*, *J. Med. Chem.* 1990, *33*, 781-789.



Formula III

Formula I

Hence, the appropriate 2-aroylbenzoic acid (2 equivalents) and N-alkylated diamine (1 equivalent) in chlorobenzene, toluene or xylene are placed in a flask equipped with a stirrer and Dean-Stark water separator and heated at reflux until no further water is seen to separate (1-8h). The solvent is then removed by distillation and the residue cooled. The residue can be purified using standard methods.

Compounds of Formula I where R_2 is a urea or thiourea are prepared using the following method.

One equivalent of the appropriate imidazoisoindolone is reacted with one equivalent of the appropriate isocyanate or isothiocyanate in THF or xylene at a temperature ranging from 20-120°C for 1-24h. The reaction is then allowed to cool and the product filtered, washed and generally recrystallised from an appropriate solvent. If no precipitate is formed the product can be purified using standard chromatographic methods.

Other compounds of formula I can be prepared by the addition, removal or modification of existing substituents. This could be achieved by using standard techniques for functional group inter-conversion, well known in the industry such as those described in Comprehensive organic transformations: a guide to functional group preparations by Larock R C, New York, VCH Publishers, Inc. 1989.

Examples of functional group inter-conversions are: -C(O)NR'R" from $-CO_2CH_3$ by heating with or without catalytic metal cyanide, e.g. NaCN, and HNR'R" in CH_3OH; -OC(O)R from –OH with e.g., ClC(O)R in pyridine; -NC(S)NR'R" from –NHR with an alkylisothiocyanate or thiocyanic acid; -NRC(O)OR' from –NHR with alkyl chloroformate; -NRC(O)NR'R" from –NHR by treatment with an isocyanate, e.g. HN=C=O or RN=C=O; -NRC(O)R' from –NHR by treatment with ClC(O)R' in pyridine; -C(=NR)NR'R" from –C(NR'R")SR with $H_3NR^+OAc^-$ by heating in alcohol; -C(NR'R")SR from –C(S)NR'R" with R-I in an inert solvent, e.g. acetone; -C(S)NR'R" (where R' or R" is not hydrogen) from $-C(S)NH_2$ with HNR'R"; -C(=NCN)-NR'R" from –C(=NR'R")-SR with NH_2CN by heating in anhydrous alcohol, alternatively from –C(=NH)-NR'R" by treatment with BrCN and NaOEt in EtOH; -NR-C(=NCN)SR from –NHR' by treatment with $(RS)_2C=NCN$; -NR"SO_2R from –NHR' by treatment with $ClSO_2R$ by heating in pyridine; -NR'C(S)R from –NR'C(O)R by treatment with Lawesson's reagent [2,4-*bis*(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide]; $-NRSO_2CF_3$ from –NHR with triflic anhydride and base, $-CH(NH_2)CHO$ from $-CH(NH_2)C(O)OR'$ with Na(Hg) and HCl/EtOH; $-CH_2C(O)OH$ from –C(O)OH by treatment with $SOCl_2$ then CH_2N_2 then H_2O/Ag_2O; -C(O)OH from $-CH_2C(O)OCH_3$ by treatment with PhMgX/HX then acetic anhydride then CrO_3; R-OC(O)R' from RC(O)R' by R"CO_3H; $-CCH_2OH$ from -C(O)OR' with Na / R'OH; $-CHCH_2$ from $-CH_2CH_2OH$ by the Chugaev reaction; $-NH_2$ from –C(O)OH by the Curtius reaction; $-NH_2$ from –C(O)NHOH with TsCl/base then H_2O; -CHC(O)CHR from –CHCHOHCHR by using the Dess-Martin Periodinane regent or CrO_3 / aqH_2SO_4 / acetone; $-C_6H_5CHO$ from $-C_6H_5CH_3$ with CrO_2Cl_2; -CHO from –CN with $SnCl_2$ / HCl; -CN from –C(O)NHR with PCl_5; $-CH_2R$ from –C(O)R with N_2H_4 / KOH.

During the reactions a number of the moieties may need to be protected. Suitable protecting groups are well known in industry and have been described in many references such as Protecting Groups in Organic Synthesis, Greene T W, Wiley-Interscience, New York, 1981.

The abbreviations that may be used herein, including in Schemes I-II, and experimental section are as follows unless indicated otherwise:

Et:	ethyl
EtOAc:	ethyl acetate
Me:	methyl
MeOH:	methyl alcohol
Ph:	phenyl
HPLC:	high performance liquid chromatography
TEA:	triethylamine
THF:	tetrahydrofuran
TsCl:	Tosyl chloride
TsOH:	Toluenesulphonic acid

The invention also pertains to therapeutic compositions containing at least one compound of formula I including pharmaceutical acceptable salts or prodrugs.

The compositions may further contain one or more other compounds having anti-viral activity in respect of RSV, such as Virazole, or other agents such as RespiGam or Synagis.

The term "composition" is intended to include the formulation of an active ingredient with encapsulating material as carrier, to give a capsule in which the active ingredient (with or without other carrier) is surrounded by carriers.

The pharmaceutical compositions or formulations include those suitable for oral, rectal, nasal, topical (including buccal and sub-lingual), vaginal or parenteral (including intramuscular, sub-cutaneous and intravenous) administration or in a form suitable for administration by inhalation or insufflation.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use.

Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Formulations containing ten (10) milligrams of active ingredient or, more broadly, 0.1 to one hundred (100) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of the present invention can be administrated in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a compound of the invention or a pharmaceutically acceptable salt of a compound of the invention.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispensable granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilisers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid that is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate,

talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as admixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized moulds, allowed to cool, and thereby to solidify.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

Sterile liquid form compositions include sterile solutions, suspensions, emulsions, syrups and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent or a mixture of both.

The compositions according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulation agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilisation from solution, for constitution with a suitable vehicle, eg. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilising and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations that are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilising agents, and the like.

For topical administration to the epidermis the compounds according to the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Formulations suitable for topical administration in the mouth include lozenges comprising active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerin or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The formulations may be provided in single or multidose form. In the latter case of a dropper or pipette, this may be achieved by the patient administering an appropriate, predetermined volume of the solution or suspension. In the case of a spray, this may be achieved for example by means of a metering atomising spray pump. To improve nasal delivery and retention the compounds according to the invention may be encapsulated with cyclodextrins, or formulated with other agents expected to enhance delivery and retention in the nasal mucosa.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In formulations intended for administration to the respiratory tract, including intranasal formulations, the compound will generally have a small particle size for example of the order of 5 to 10 microns or less. Such a particle size may be obtained by means known in the art, for example by micronisation.

When desired, formulations adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

The invention also includes the compounds in the absence of carrier where the compounds are in unit dosage form.

The amount of compound of formula I administered may be in the range from about 10 mg to 2000 mg per day, depending on the activity of the compound and the disease to be treated.

Liquids or powders for intranasal administration, tablets or capsules for oral administration and liquids for intravenous administration are the preferred compositions.

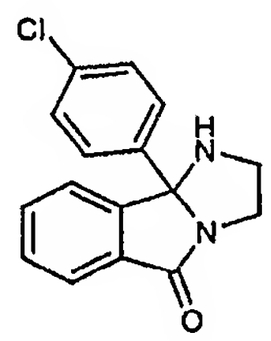
Experimental Data

^{1}H NMR spectra were recorded on either a Bruker Avance DRX 400, AC 200 or AM 300 spectrometer. Spectra were recorded in $CDCl_3$, d_6-acetone, CD_3OD or d_6-DMSO using the residual solvent peak as a reference. Chemical shifts are reported on the δ scale in parts per million (ppm) using the following conventions to assign the multiplicity: s (singlet), d (doublet), t (triplet), q (quartet) m (multiplet) and prefixed b (broad). Mass spectra (ESI) were recorded on either a Micromass Platform QMS or Finnigan LCQ Advantage spectrometer. Flash chromatography was performed on 40-63μm silica gel 60 (Merch No. 9385). Analytical HPLC was carried out using a Waters 600 Pump, Waters 717 Autosampler and a Waters 490E UV detector. Preparative HPLC was carried out using a Gilson 322 pump with a Gilson 215 liquid handler and a HP1100 PDA detector. Both HPLC systems employed Phenomonex C8(2) columns using either acetonitrile or acetonitrile containing 0.06% TFA in water or water containing 0.1% TFA.

Method A

One equivalent of an appropriate 2-(Aroyl)benzoic acid of formula III, is reacted with approximately 3 equivalents of an appropriate diamine of the general formula H_2N-B-C-NH_2. The mixture is heated under reflux in an inert solvent, such as toluene or xylene, with a Dean-Stark apparatus for 3-10 h. A catalyst, such as an acid tosylate, can be used. After this time the reaction is allowed to cool and the product filtered and recrystallised from an appropriate solvent. In no precipitate forms the solvent is evaporated *in-vacuo* and the residue recrystallised or purified using flash chromatography or preparative HPLC.

Compound 1

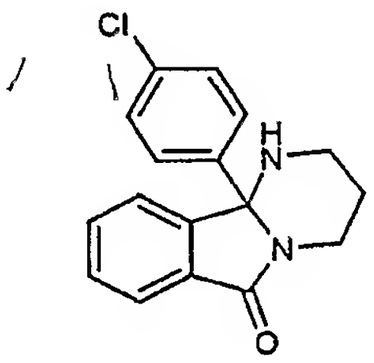


Compound **1** was prepared using **Method A** employing 2-(4-chlorobenzoyl)benzoic acid and ethylene diamine.

^{1}H NMR (300MHz, $CDCl_3$) δ 2.05 (bs, 1H), 3.11-3.26 (m, 2H), 3.61-3.68 (m, 1H), 3.76-3.84 (m, 1H), 7.22-7.26 (m, 1H), 7.30 (d, *J* 8.9 Hz, 2H), 7.42-7.48 (m, 2H), 7.62 (d, *J* 8.8 Hz, 2H), 7.74-7.80 (m, 1H).

MS m/z 285 ([M+H$^+$]

Compound 2

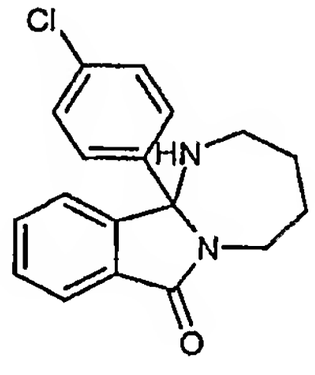


Compound **2** was prepared using **Method A** from 2-(4-chlorobenzoyl)benzoic acid and 1,3-diaminopropane.

^{1}H NMR (300MHz, $CDCl_3$) δ 1.48-1.62 (m, 2H), 2.83-2.96 (m, 1H), 2.97-3.13 (m, 2H), 4.47-4.60 (m, 1H), 7.22-7.29 (m, 1H), 7.31-7.37 (m, 2H), 7.38-7.47 (m, 2H), 7.48-7.56 (m, 2H), 7.82-7.89 (m, 1H).

MS m/z ([M+H$^+$] 299

Compound 7



Compound **7** was prepared using **Method A** from 2-(4-chlorobenzoyl)benzoic acid and 1,4-diaminobutane.

^{1}H NMR (300MHz, $CDCl_3$) δ 1.13-1.32 (m, 2H), 1.33-1.57 (m, 2H), 2.15-2.44 (m, 2H), 2.73-2.90 (m, 1H), 3.32-3.49 (m, 1H), 7.10-7.20 (m, 1H), 7.21-7.34 (m, 4H), 7.35-7.49 (m, 2H), 7.60-7.71 (m, 1H).

MS m/z ([M+H$^+$] 313

The methods for forming intermediate IV are based on those described in US 4,058,529, Sulkowski, T.S., *et. al*, *J. Org. Chem.* **1967**, *32*, 2180-2184 and Houlihan, W.J. , *et. al*, *J. Med. Chem.* **1975**, *18*, 182-185.

Method B

Two equivalents of diisopropylethylamine or triethylamine are added to one equivalent of imidazoisoindolone in THF at 0°C. An acid chloride, or other acylating agent, is added to the mixture and the reaction monitored by HPLC. When the reaction is complete the reaction is quenched with water and the product extracted into EtOAc. The EtOAc is subsequently washed with a 1:1 solution of sat. $NH_4Cl_{(aq)}$:water, 1:1 sat. $Na_2CO_{3(aq)}$:water and sat. $Na_2CO_{3\,(aq)}$. The EtOAc was dried (Na_2SO_4), the solvent evaporated *in vacuo* and the residue either crystallised or purified by flash chromatography using EtOAc/hexanes or by preparative HPLC.

Method C

One equivalent of the appropriate imidazoisoindolone is reacted with one equivalent of the appropriate acid chloride in xylene at 120°C for 1-24h. The reaction is then allowed to

cool and the product filtered and recrystallised from an appropriate solvent. If no precipitate was formed the reaction was purified using flash chromatography or preparative HPLC.

Method D

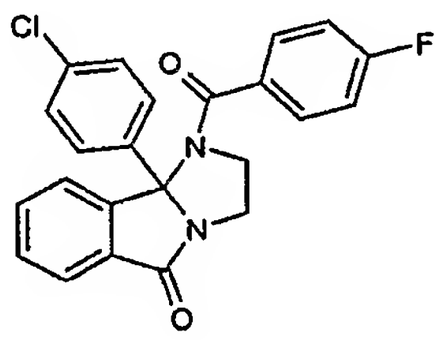
The *N*-alkylated diamines used were prepared according to the procedure outlined in Kruse L.I., *et. al*, *J. Med. Chem.* 1990, *33*, 781-789.

Appropriate 2-aroylbenzoic acid (2 equivalents) and *N*-alkylated diamine(1 equivalent) in chlorobenzene, toluene or xylene were placed in a flask equipped with a stirrer and Dean-Stark water separator. The mixture was refluxed until no further water was seen to separate (1-8h) after which time the solvent was then distilled off and the residue cooled. The residue was purified using flash chromatography or preparative HPLC.

Method E

One equivalent of the appropriate imidazoisoindolone is reacted with one equivalent of the appropriate isocyanate in THF or xylene at a temperature ranging from 20-120°C for 1-24h. The reaction is then allowed to cool and the product filtered, washed and recrystallised from an appropriate solvent. If no precipitate was formed the reaction was purified using flash chromatography or preparative HPLC.

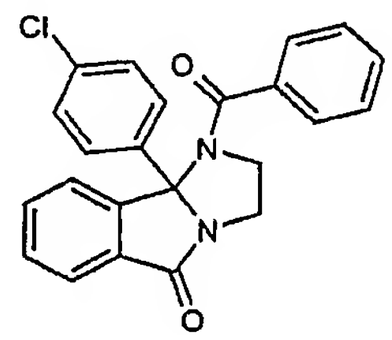
Compound 12



Compound **12** was prepared using **Method C** using Compound **1** and 4-fluorobenzoyl chloride.

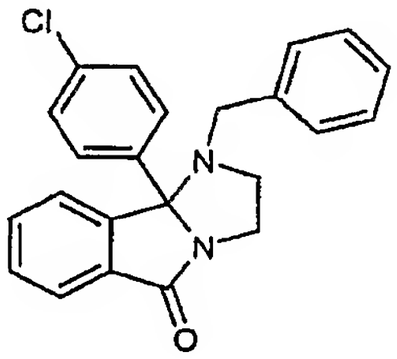
^{1}H NMR (300MHz, $CDCl_3$) δ 3.22-3.34 (m, 1H), 3.73-3.82 (m, 1H), 3.91-4.03 (m, 1H), 4.28-4.36 (m, 1H), 7.05-7.13 (m, 2H), 7.17 (d, *J* 7.8 Hz, 2H), 7.33 (d, *J* 7.8 Hz, 2H), 7.43-7.52 (m, 2H), 7.54-7.65 (m, 2H), 7.84-7.90 (m, 1H), 8.00-8.06 (m, 1H).
MS m/z 407 ([M+H$^+$]

Compound 13



Compound **13** was prepared using **Method C** using Compound **1** and benzoyl chloride.
^{1}H NMR (300MHz, $CDCl_3$) δ 3.21-3.31 (m, 1H), 3.72-3.79 (m, 1H), 3.91-4.00 (m, 1H), 4.26-4.33 (m, 1H), 7.20 (d, *J* 8.8 Hz, 2H), 7.34 (d, *J* 8.8 Hz, 2H), 7.38-7.48 (m, 5H), 7.56-7.61 (m, 2H), 7.85-7.88 (m, 1H), 8.04-8.07 (m, 1H).
MS m/z 389 ([M+H$^+$]

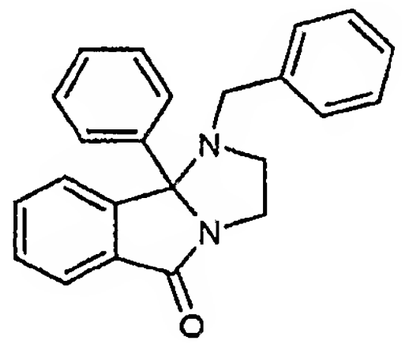
Compound 23



Compound **23** was prepared using **Method D** from 2-(4-chlorobenzoyl)benzoic acid and *N*-benzyl ethylenediamine.

^{1}H NMR (300MHz, $CDCl_3$) δ 2.97 (d, J_{AB} 13Hz, 1H), 3.07-3.32 (m, 3H), 3.42 (d, J_{AB} 13Hz, 1H), 3.83-3.96 (m, 1H), 7.04-7.09 (m, 1H), 7.17-7.38 (m, 8H), 7.39-7.46 (m, 1H), 7.66-7.73 (m, 2H), 7.81-7.86 (m, 1H).
MS m/z ([M+H$^+$] 375

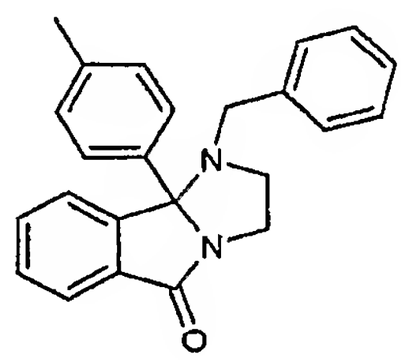
Compound 24



Compound **24** was prepared using **Method D** from 2-benzoylbenzoic acid and *N*-benzyl ethylenediamine.

^{1}H NMR (300MHz, $CDCl_3$) δ 2.99 (d, J_{AB} 13Hz, 1H), 3.10-3.29 (m, 3H), 3.44 (d, J_{AB} 13Hz, 1H), 3.84-3.99 (m,1H), 7.07-7.13 (m, 1H), 7.18-7.44 (m, 10H), 7.73-7.81 (m, 2H), 7.82-7.87 (m, 1H).
MS m/z ([M+H$^+$] 341

Compound 25



Compound **25** was prepared using **Method D** from 2-(4-toluoyl)benzoic acid and *N*-benzyl ethylenediamine.

^{1}H NMR (300MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.00 (d, J_{AB} 13Hz, 1H), 3.11-3.29 (m, 3H), 3.45 (d, J_{AB} 13Hz, 1H), 3.86-3.98 (m, 1H), 7.08-7.14 (m, 1H), 7.15-7.21 (m, 2H), 7.22-7.44 (m, 7H), 7.63-7.69 (m, 2H), 7.81-7.86 (m, 1H).
MS m/z ([M+H$^+$] 355

Compound 106

Compound 106 was prepared using Method A employing 3-bromo-(4-chlorobenzoyl)benzoic acid and ethylene diamine.

1H NMR (300 MHz, CDCl3): δ 3.12-3.25 (m, 2H), 3.64-3.71 (m, 1H), 3.76-3.83 (m, 1H), 7.13, (dd, J 8.1, 0.6 Hz, 1H), 7.33 (d, J 8.7 Hz, 2H), 7.57-7.61 (m, 3H), 7.91 (dd, J 1.8, 0.6 Hz, 1H).
MS m/z ([M+H]+) 365

Compound 107

Compound 107 was prepared using Method A employing 4-bromo-(4-chlorobenzoyl)benzoic acid and ethylene diamine.

1H NMR (300 MHz, CDCl3): δ 3.11-3.24 (m, 2H), 3.69-3.63 (m, 1H), 3.76-3.82 (m, 1H), 7.34, (d, J 8.7 Hz, 1H), 7.39 (dd, J 1.5, 0.6 Hz, 1H), 7.59-7.66 (m, 4H).
MS m/z ([M+H]+) 365

Method F

Two equivalents of boronic acid, five equivalents of Na_2CO_3 and palladium on charcoal (catalytic) or 0.1 equivalents of [PdCl2(dppf)] (dichloro[1,1'-bis (diphenylphosphino) ferrocene]palladium (II) dichloromethane adduct) are added to the appropriate bromo-imidazoisoindolone in DME/H2O (93:7). The reaction is heated to 50°C for 1-4h. The reaction is then cooled, filtered and evaporated in vacuo to give a solid or oily residue. The residue is then either recrystallised or purified by flash chromatography using EtOAc/hexanes or by preparative HPLC.

Method G

Three equivalents of boronic acid, six equivalents of K_2CO_3 and 0.3 equivalents of tetrakis(tripheynylphosphine)palladium are added to the appropriate bromo-imidazoisoindolone in toluene. The reaction is heated to 100°C for 1-24h. The reaction is then quenched with CH_2C_{l2} and washed with water. The CH_2C_{l2} layer was dried (Na_2SO_4) and evaporated in vacuo to give a solid or oily residue. The residue is then either recrystallised or purified by flash chromatography using EtOAc/hexanes or by preparative HPLC.

Method H

The acid chloride or anhydride (2.2eq) was added directly for liquids or as a solution in pyridine (~1M) for solids to a solution of the appropriate amine or alcohol (0.1mmol) in pyridine (500µL) at -5°C. The reaction was stirred and allowed to warm to room temparature for between 2-24h after which time the starting material has been consumed. The reaction was subsequently diluted with water and extracted with CH_2C_{l2} (3x). The combined CH_2C_{l2} extracts were washed with 1N NaOH (3x) and 10% HCl (3x). In the case of basic products the acid wash was omitted and in the case of acidic products the basic wash was omitted. For neutral or basic products the crude purity was improved markedly by stirring the combined CH_2C_{l2} extract in the presence of a carbonate resin (MP-Carbonate ~3eq) for 0.5-12h. The CH_2C_{l2} extracts were dried ($MgSO_4$) and the solvent evaporated in-vacuo. The crude products were subsequently purified by flash chromatography using a EtOAc/Hexane solvent system.

Compound 120

Compound 120 was prepared using Method F employing compound 107 and 4-tolylboronic acid.

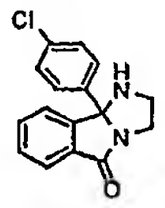
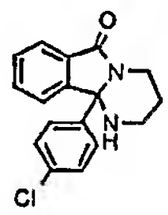
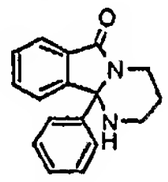
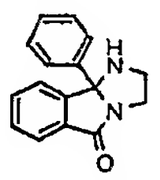
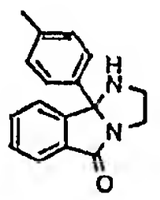
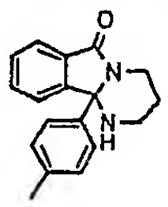
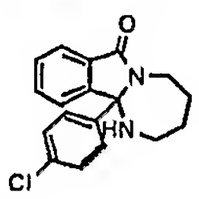
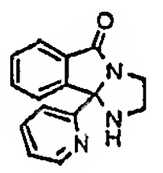
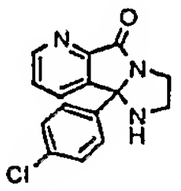
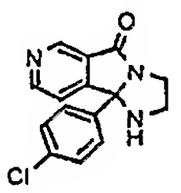
1H NMR (300 MHz, CDCl3): δ 3.19-3.26 (m, 2H), 3.65-3.72 (m, 1H), 3.86-3.89 (m, 1H), 7.23, (d, J 8.1 Hz, 2H), 7.34 (d, J 8.7 Hz, 2H), 7.39-7.45 (m, 3H), 7.65-7.71 (m, 3H), 7.82 (dd, J 8.1, 0.6 Hz, 4H).
MS m/z ([M+H]+) 375

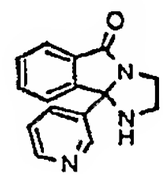
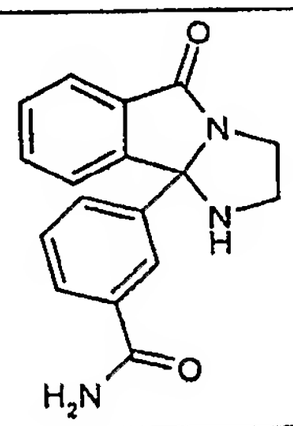
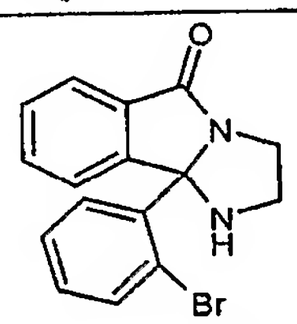
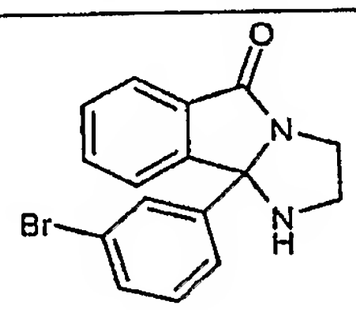
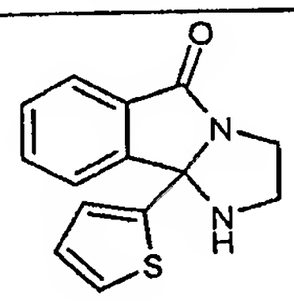
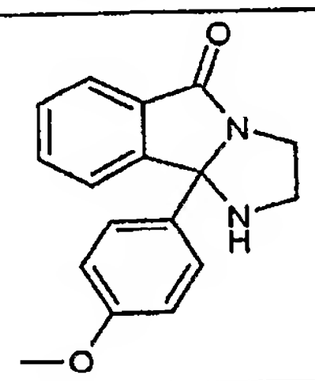
Compound 132

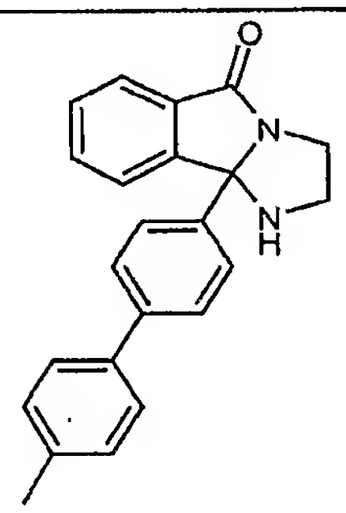
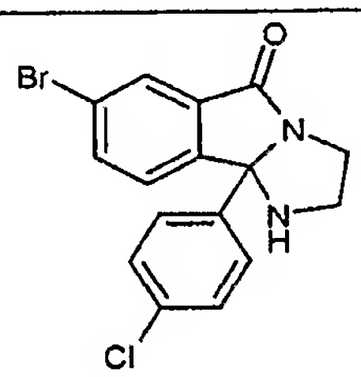
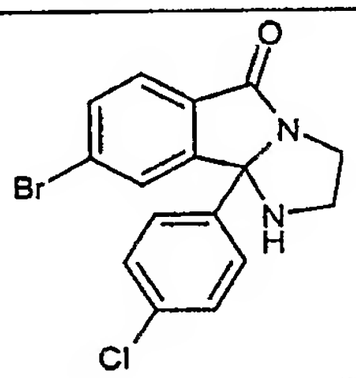
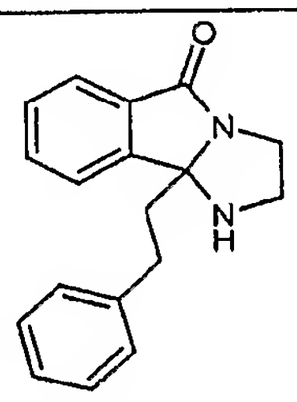
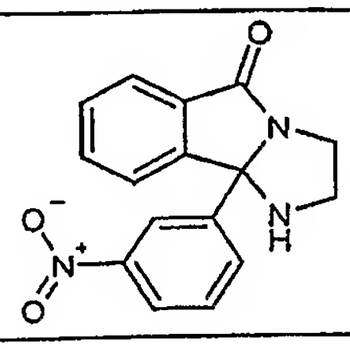
Compound 132 was prepared using Method G employing compound 107 and n-butylboronic acid.

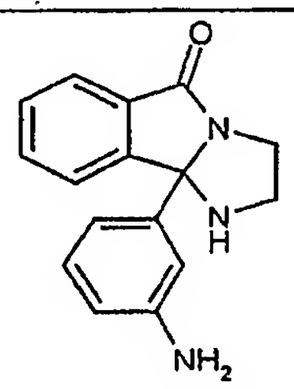
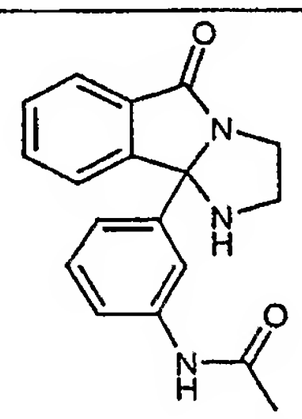
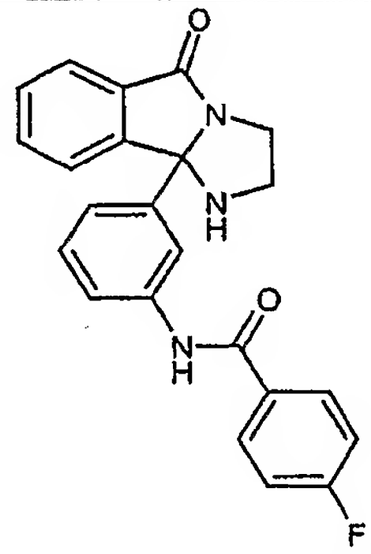
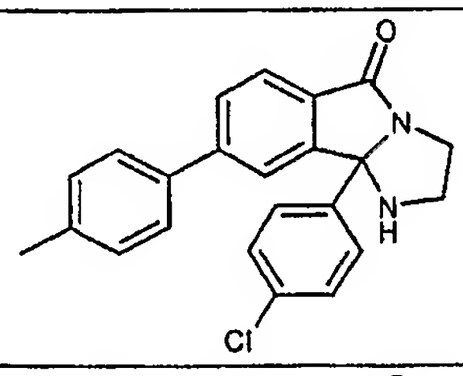
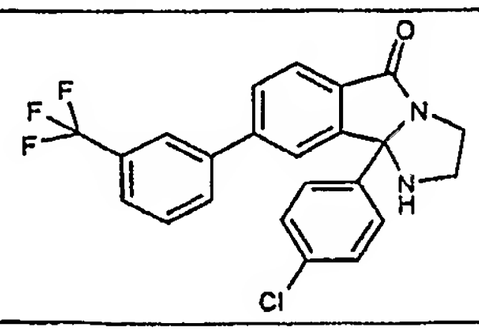
1H NMR (300 MHz, CDCl3): δ 0.89 (t, J 7.5 Hz, 3H), 1.23-1.37 (m, 3H), 1.48-1.56 (m, 2H), 2.59 (t, J 7.8 Hz, 2H), 3.12-3.26 (m, 2H), 3.62-3.69 (m, 1H), 3.83-3.78 (m, 1H), 7.26-7.35 (m, 3H), 7.62-7.69 (m, 3H).
MS m/z ([M+H]+) 341

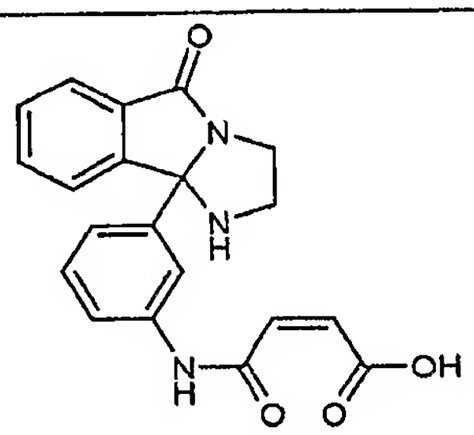
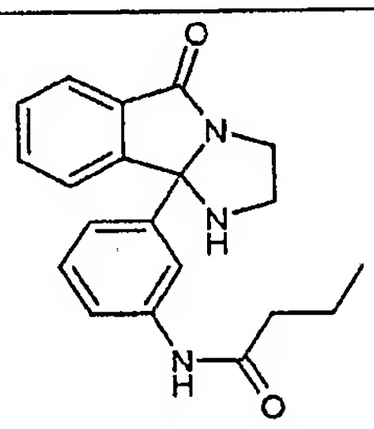
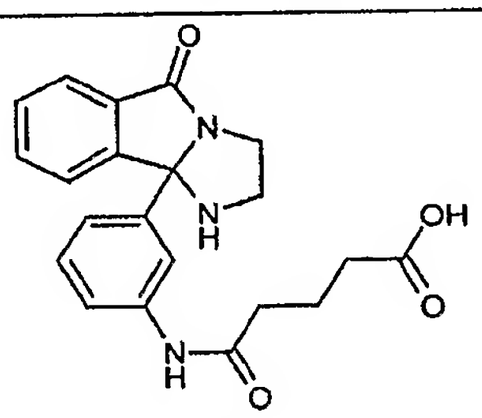
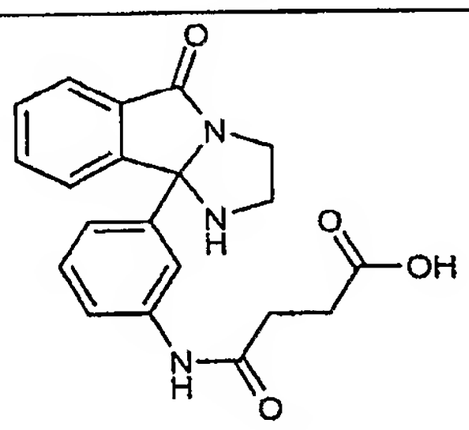
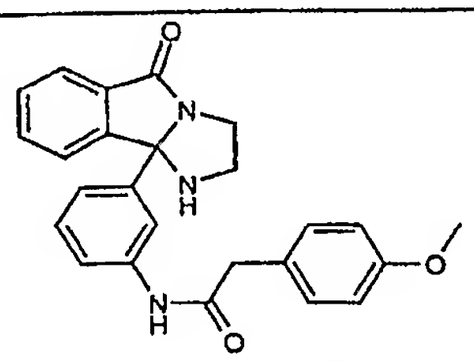
Table 1: Compounds of Formula I where R_2 is H

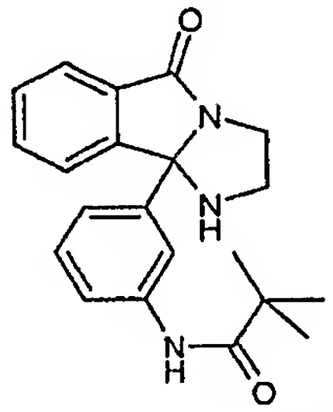
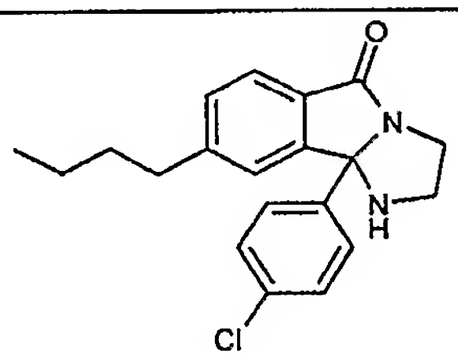
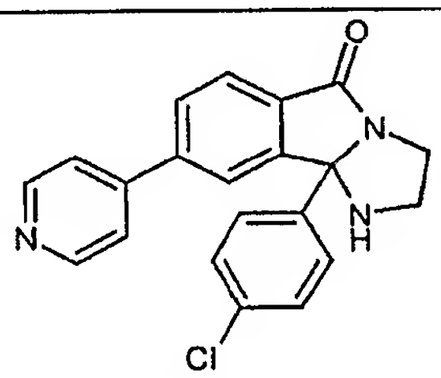
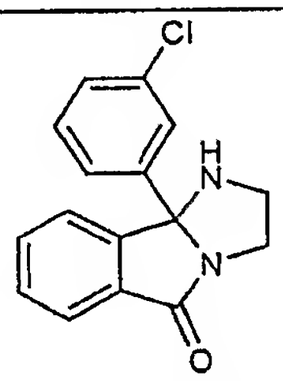
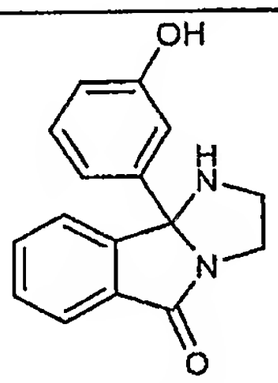
Cmpd N°	Structure	m/z [M+H+]	Prep Method
1		285	A
2		299	A
3		265	A
4		251	A
5		265	A
6		279	A
7		313	A
8		252	A
9		286	A
10		286	A

Cmpd N°	Structure	m/z [M+H$^+$]	Prep Method
11		252	A
95			A
96		331	A
97		331	A
100		257	A
102		281	A

Cmpd N°	Structure	m/z [M+H+]	Prep Method
103		341	F
106		365	A
107		365	A
110		279	A
111		296	A

Cmpd N°	Structure	m/z [M+H$^+$]	Prep Method
112		266	A
115		308	H
116		388	H
120		375	F
121		423	F

Cmpd N°	Structure	m/z [M+H+]	Prep Method
122		364	H
126		336	H
127		380	H
128		366	H
130		414	B

Cmpd N°	Structure	m/z [M+H+]	Prep Method
131		350	H
132		341	G
133		362	F
134		285	A
136		267	A

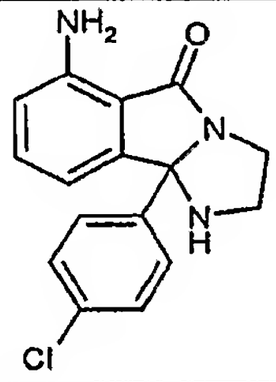
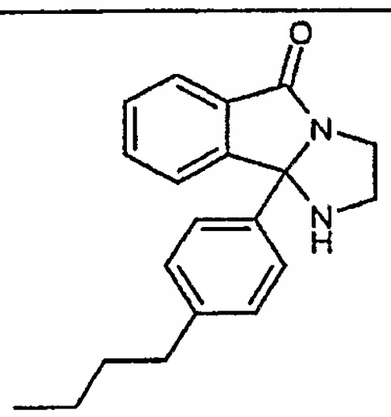
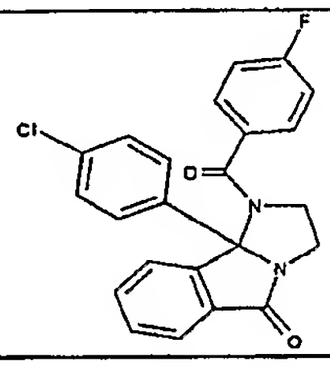
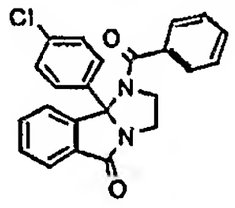
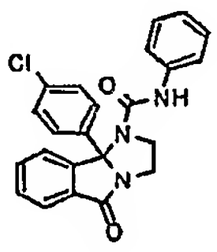
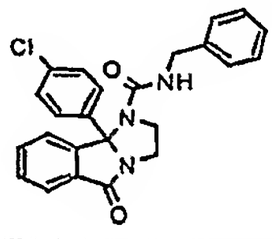
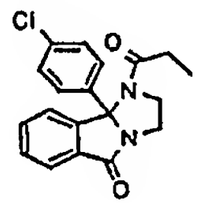
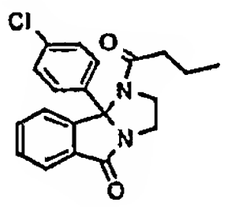
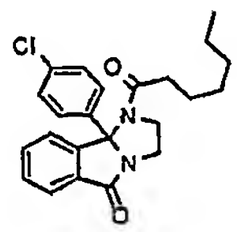
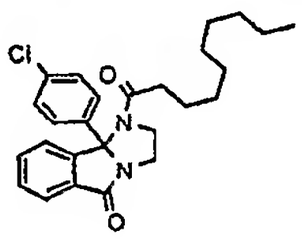
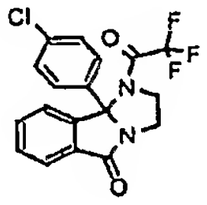
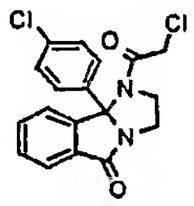
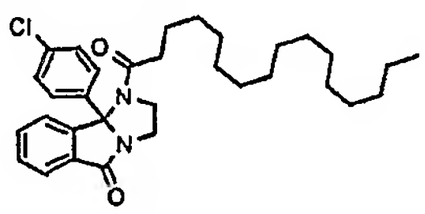
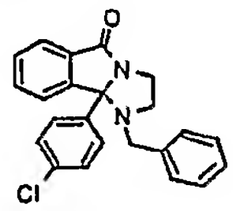
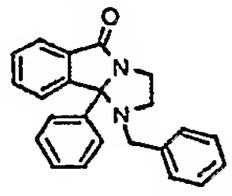
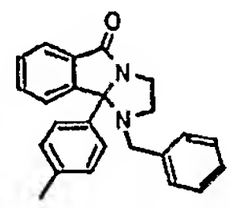
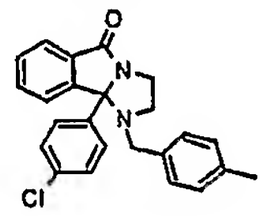
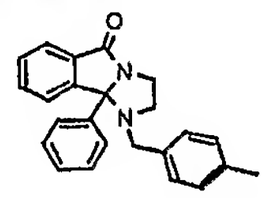
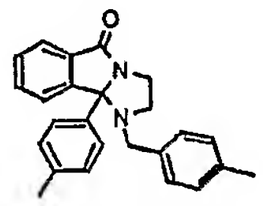
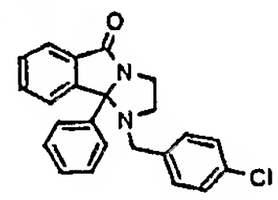
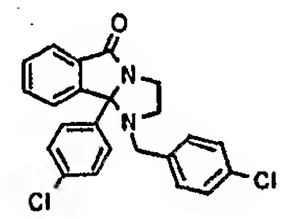
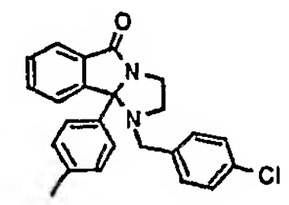
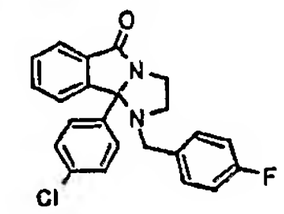
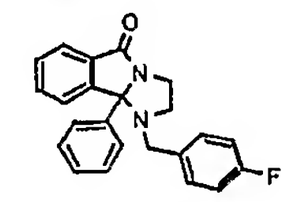
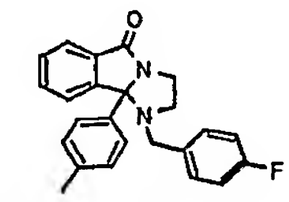
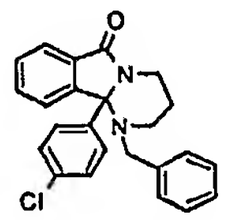
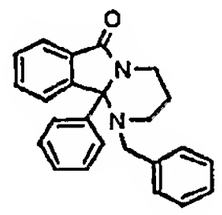
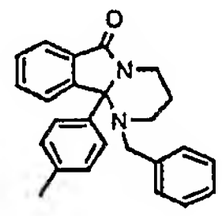
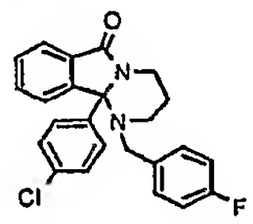
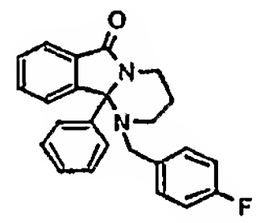
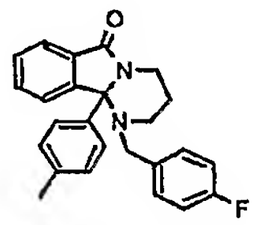
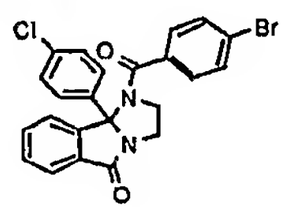
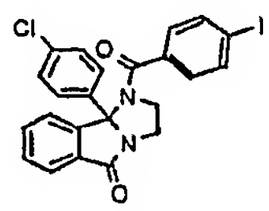
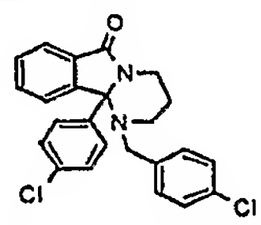
Cmpd N°	Structure	m/z [M+H$^+$]	Prep Method
140		300	A
142		307	A

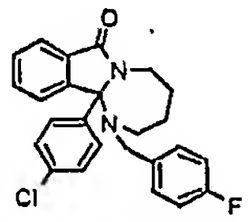
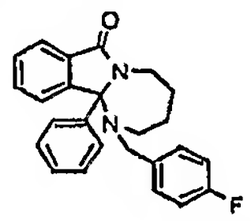
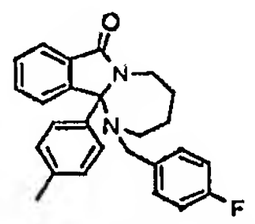
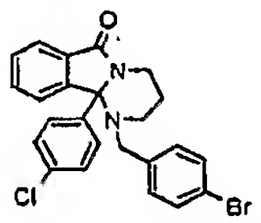
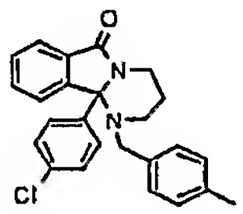
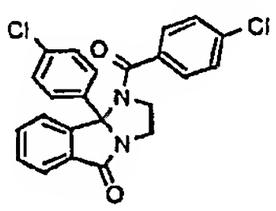
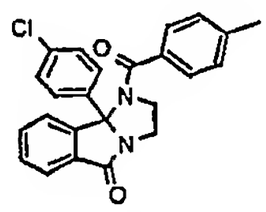
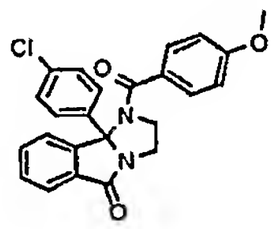
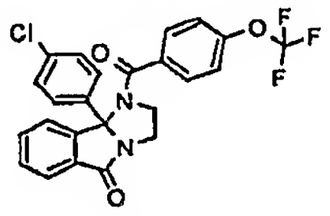
Table 2: Compounds of Formula I where R_2 is not H

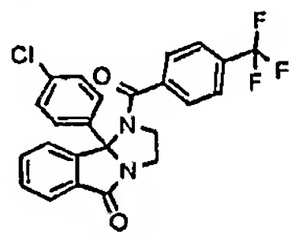
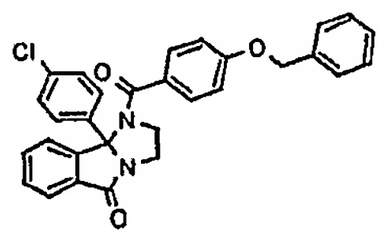
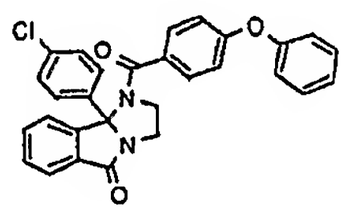
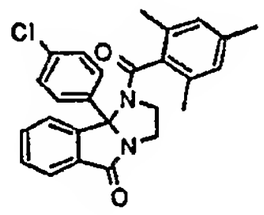
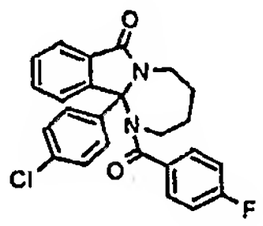
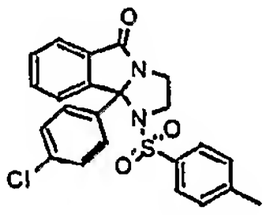
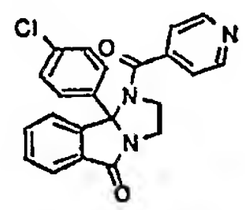
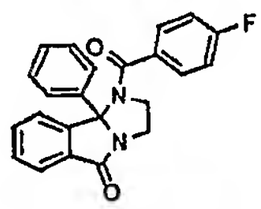
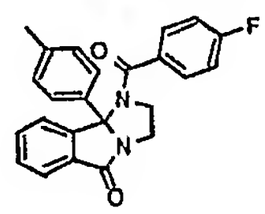
N°	Structure	m/z [M+H$^+$]	Prep Method
12		407	B
13		389	B
14		404	E
15		418	E

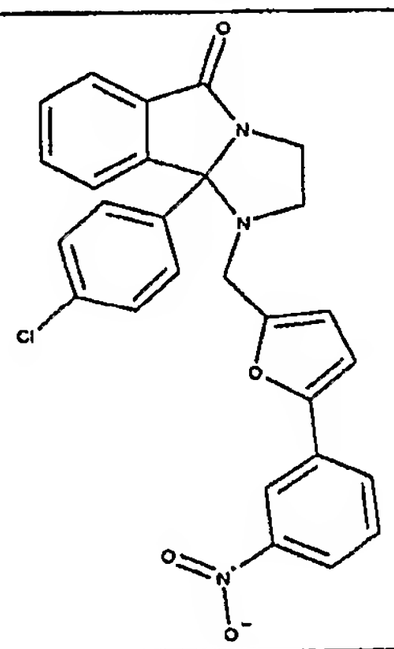
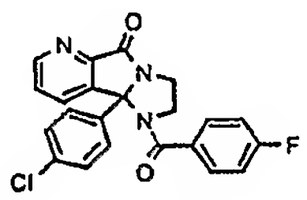
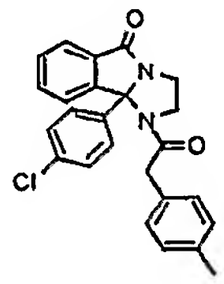
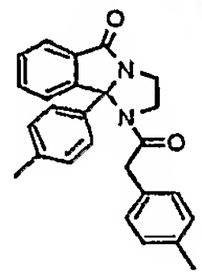
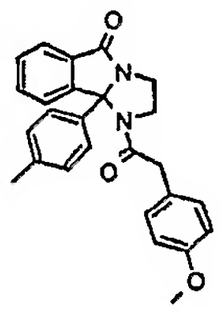
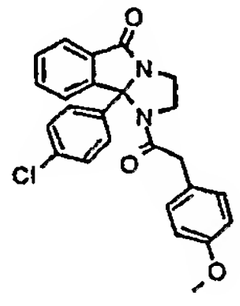
N°	Structure	m/z [M+H$^+$]	Prep Method
16		341	B
17		355	B
18		397	B
19		439	B
20		381	B
21		361	B
22		523	B
23		375	D
24		341	D

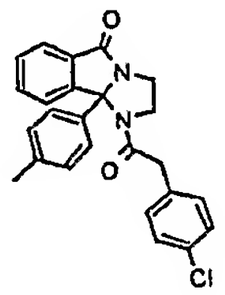
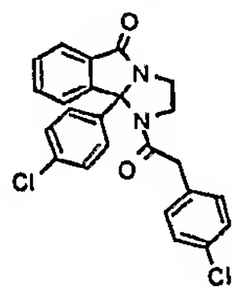
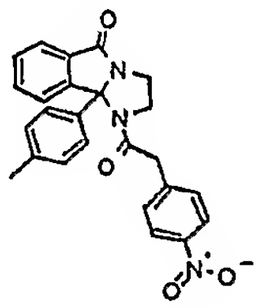
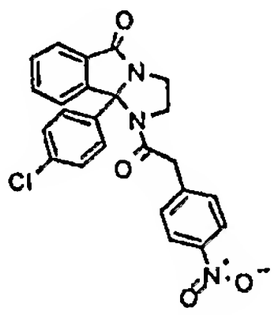
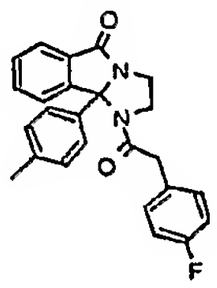
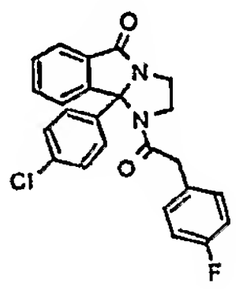
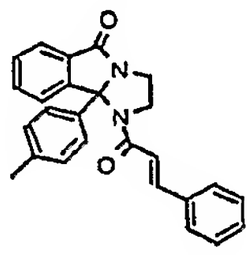
N°	Structure	m/z [M+H⁺]	Prep Method
25		355	D
26		389	D
27		355	D
28		369	D
29		375	D
30		409	D
31		389	D
32		393	D
33		359	D
34		373	D

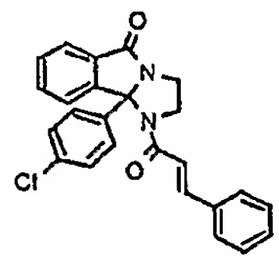
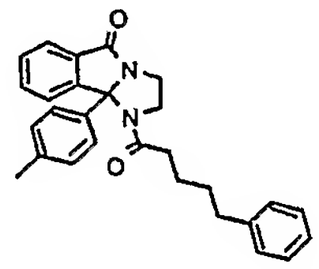
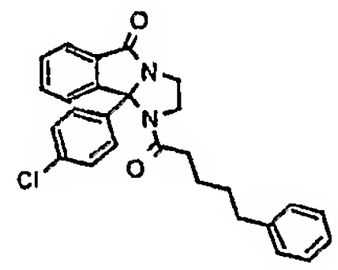
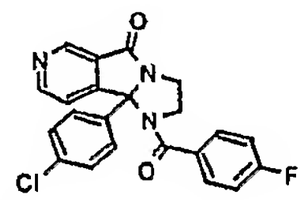
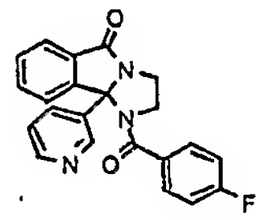
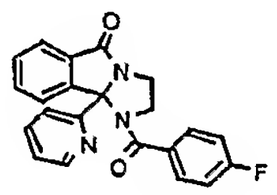
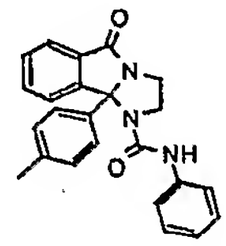
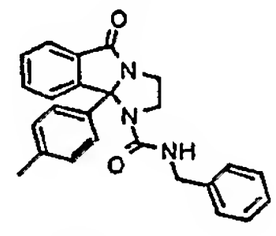
N°	Structure	m/z [M+H$^+$]	Prep Method
35		389	D
36		355	D
37		369	D
38		407	D
39		373	D
40		387	D
41		469	C
42		515	C
43		423	D

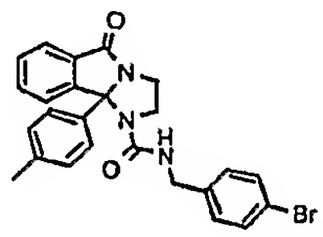
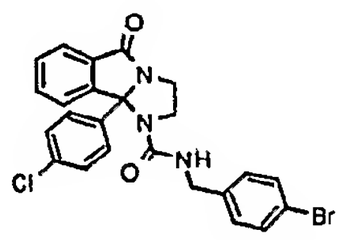
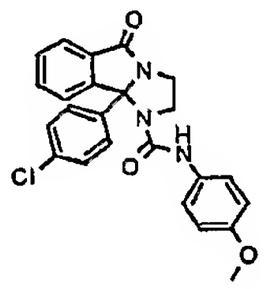
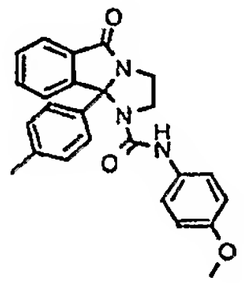
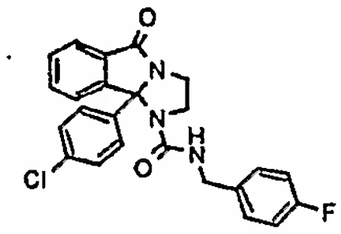
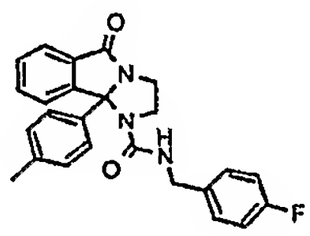
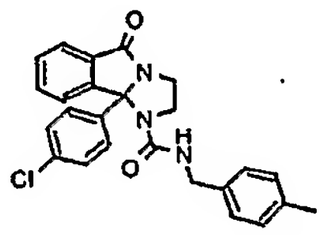
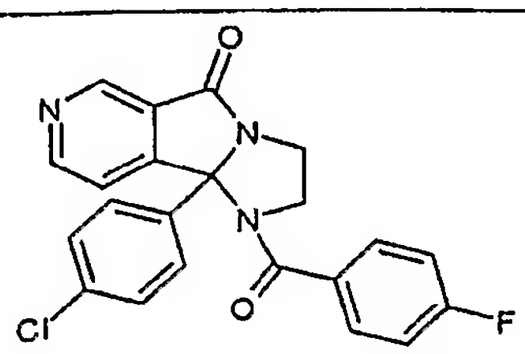
N°	Structure	m/z [M+H$^+$]	Prep Method
44		421	D
45		387	D
46		401	D
47		468	D
48		403	D
49		423	C
50		403	C
51		419	C
52		473	C

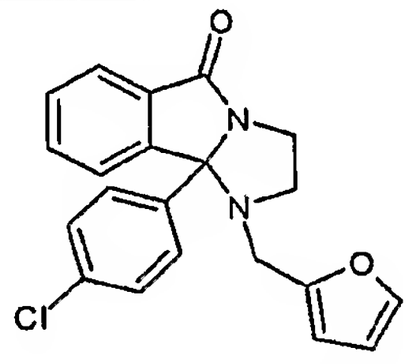
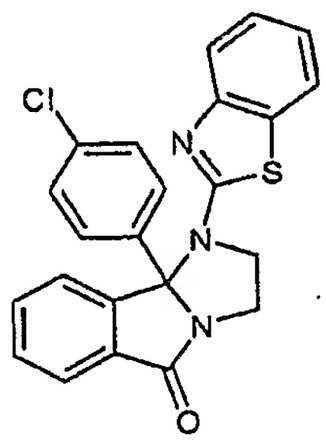
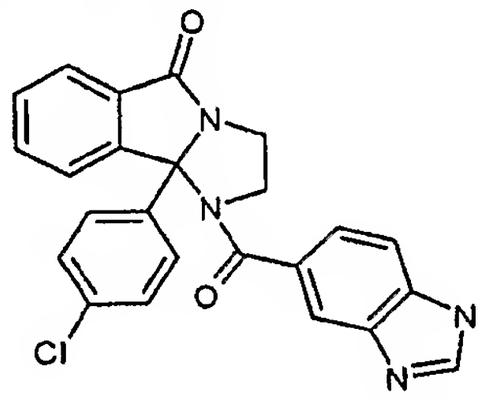
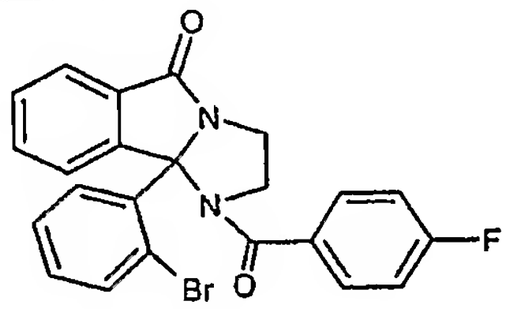
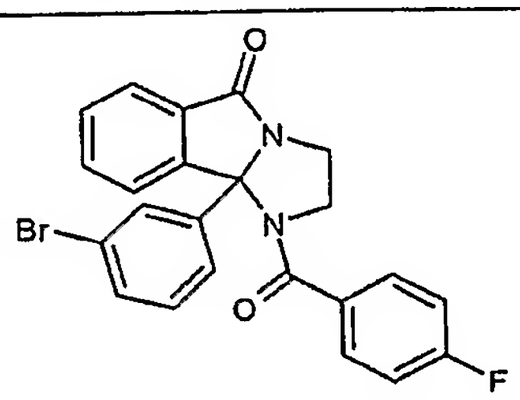
N°	Structure	m/z [M+H⁺]	Prep Method
53		457	C
54		495	C
55		481	C
56		431	C
57		435	C
58		439	D
59		390	C
60		373	C
61		387	C

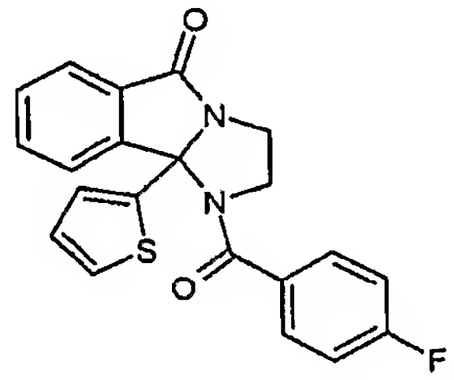
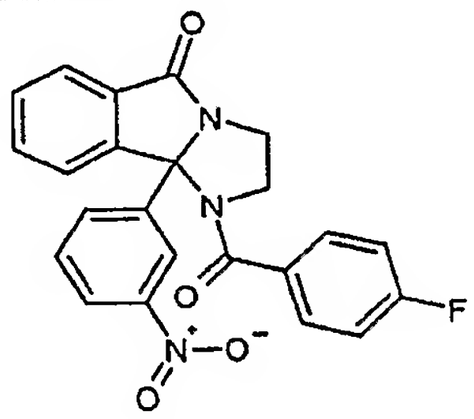
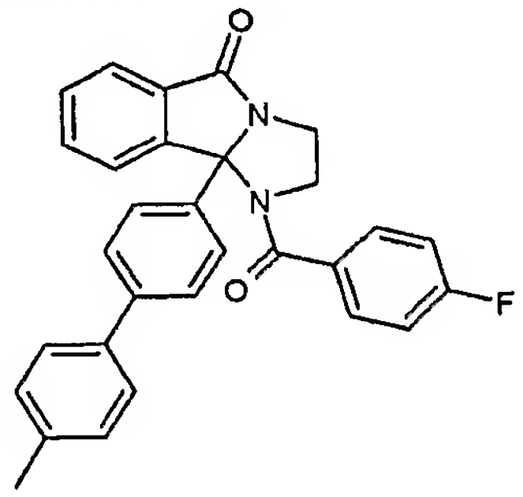
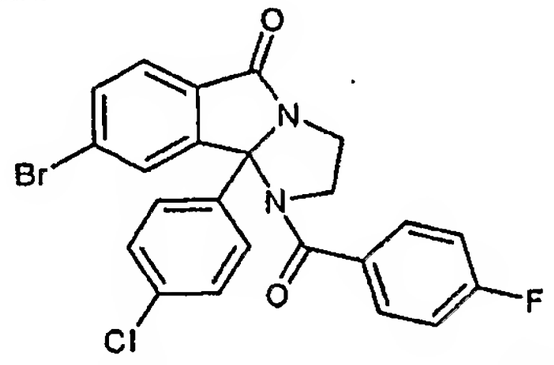
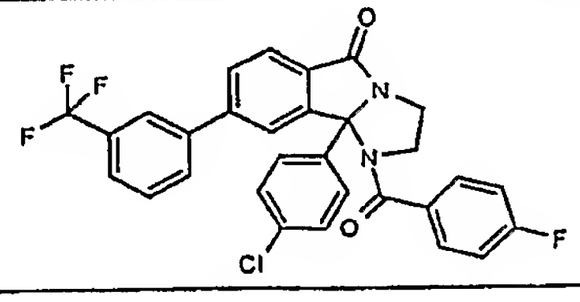
N°	Structure	m/z [M+H⁺]	Prep Method
62		486	D
63		408	C
64		417	C
65		397	C
66		413	C
67		433	C

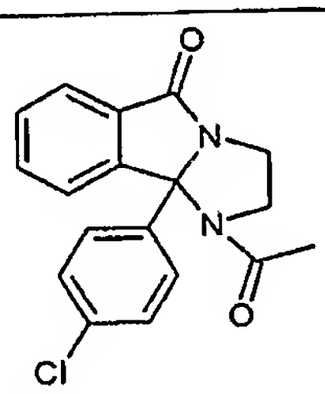
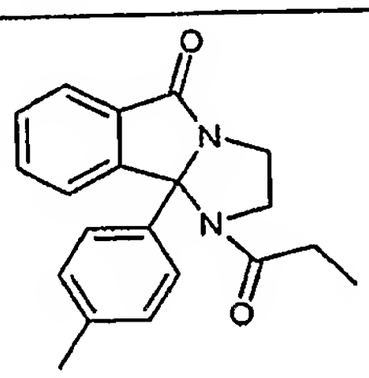
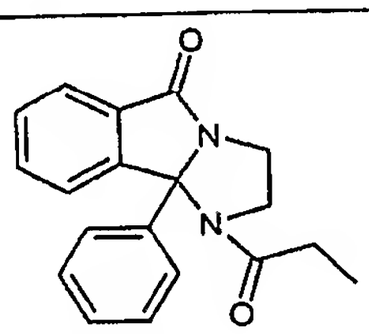
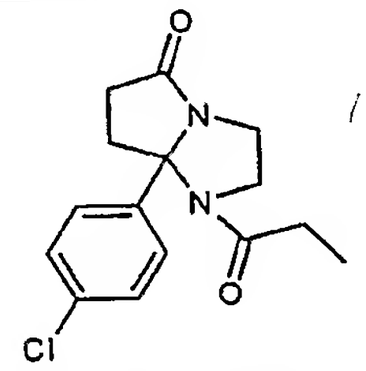
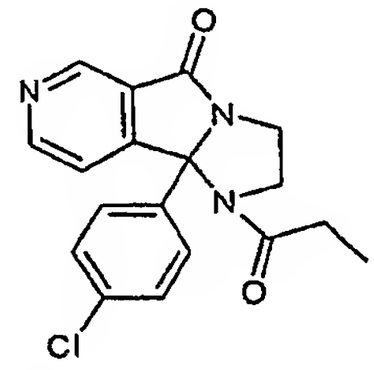
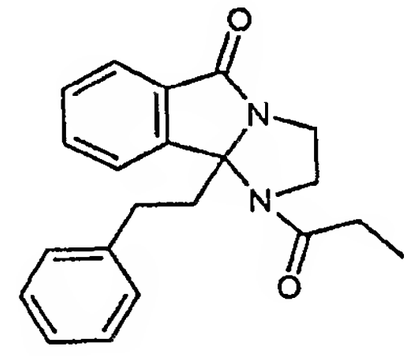
N°	Structure	m/z [M+H⁺]	Prep Method
68		417	C
69		437	C
70		428	C
71		448	C
72		401	C
73		421	C
74		395	C

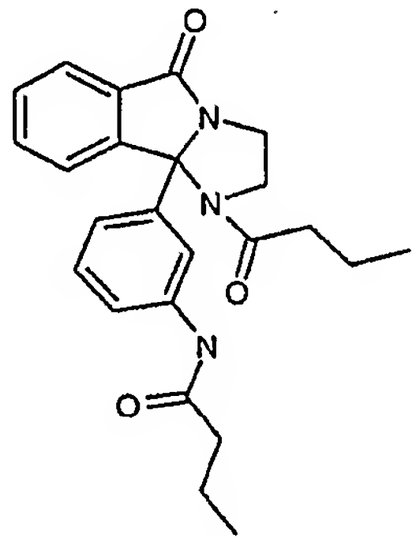
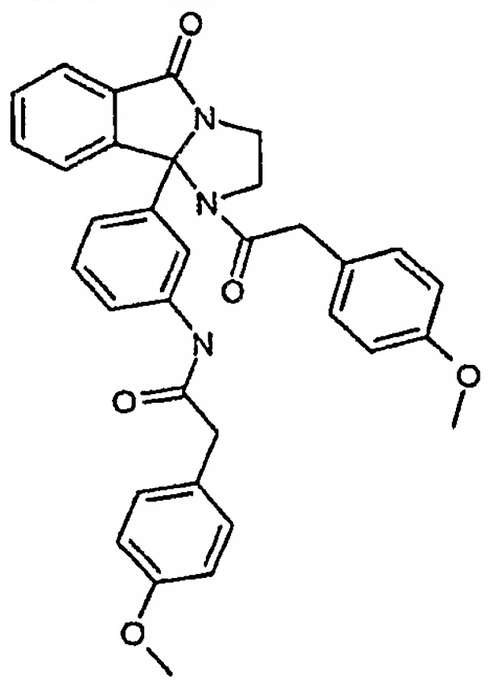
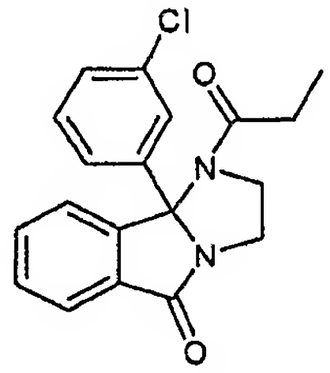
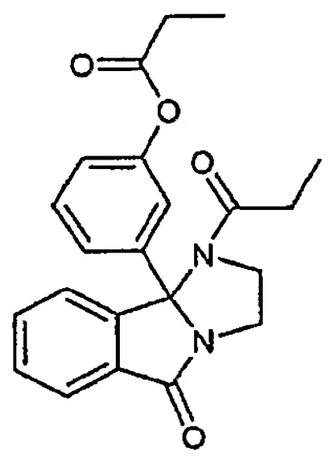
N°	Structure	m/z [M+H⁺]	Prep Method
75		415	C
76		425	C
77		445	C
78		408	C
79		374	C
80		374	C
81		384	E
82		398	E

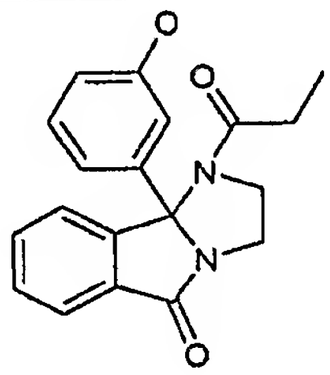
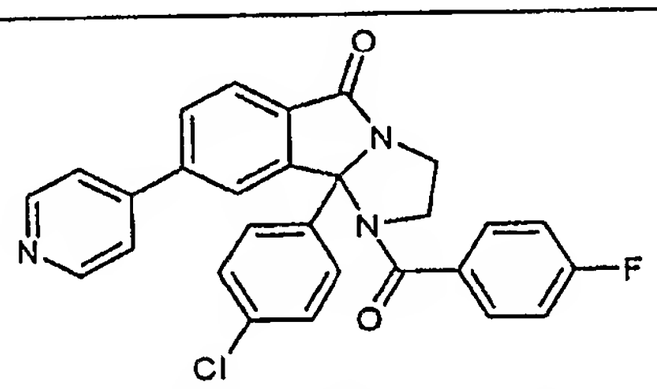
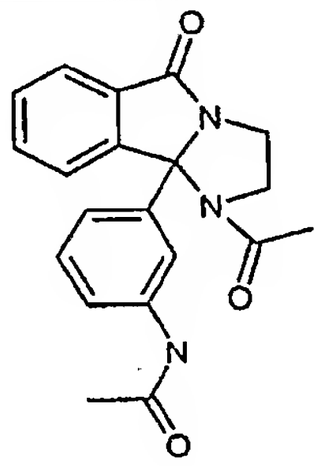
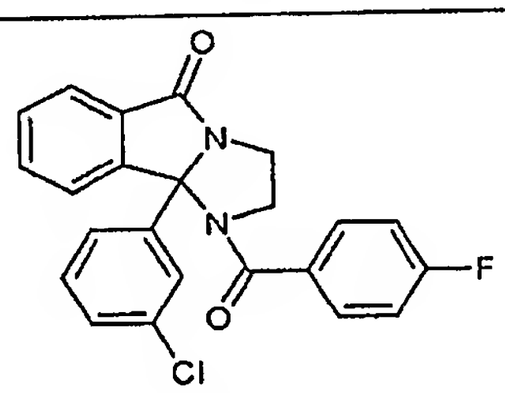
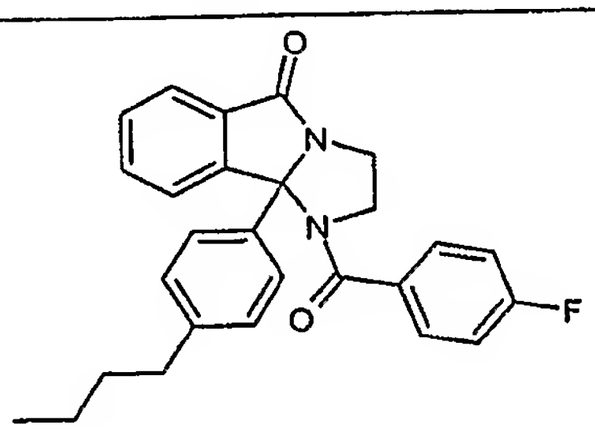
N°	Structure	m/z [M+H$^+$]	Prep Method
83		477	E
84		497	E
85		434	E
86		414	E
87		436	E
88		416	E
89		432	E
90		408	B

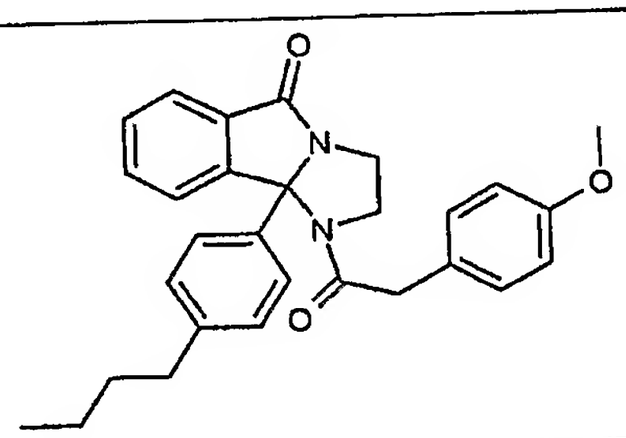
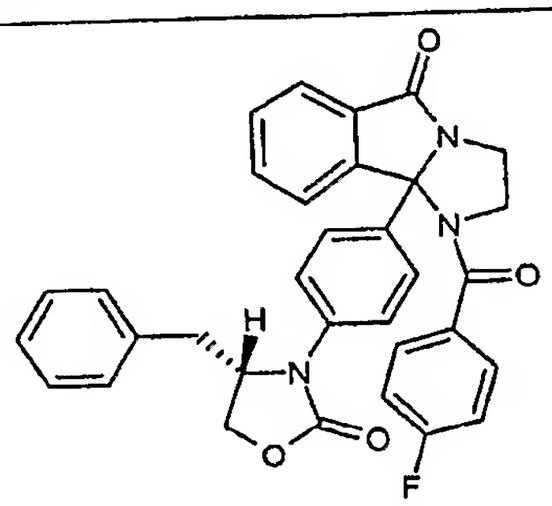
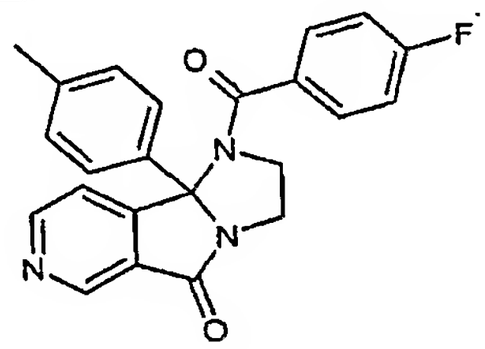
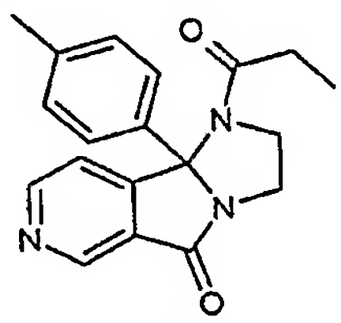
N°	Structure	m/z [M+H⁺]	Prep Method
91		365	D
92		418	D
94		429	B
98		453	B
99		453	B

N°	Structure	m/z [M+H$^+$]	Prep Method
101		379	B
104		418	B
105		463	B
108		487	B
109		551	B

N°	Structure	m/z [M+H⁺]	Prep Method
114		327	H
117		321	B
118		307	B
119		293	H
123		342	H
124		335	H

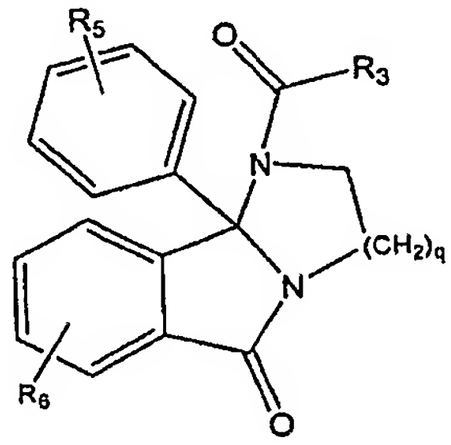
N°	Structure	m/z [M+H⁺]	Prep Method
125		406	H
129		562	H
135		341	H
137		379	H

N°	Structure	m/z [M+H$^+$]	Prep Method
138		323	Alkaline hydrolysis of 137
139		484	B
143		350	H
144		407	H
145		429	H

N°	Structure	m/z [M+H+]	Prep Method
146		455	H
147		548	H
148		388	H
149		322	H

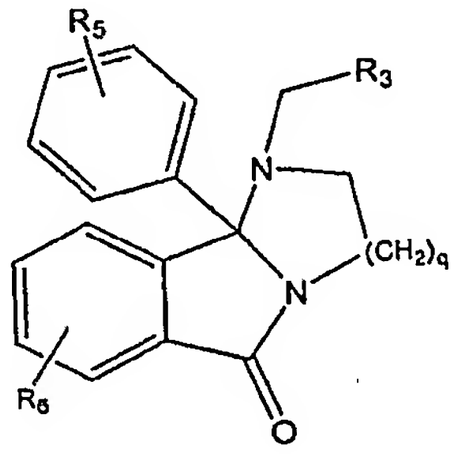
Examples of other specific compounds within the scope of the invention are shown in the following tables.

Table 3



R_3	R_5	R_6	q
p Et-C_6H_4-	H	H	1
furyl	p Me	H	1
imidazolyl	p Cl	p Cl	1
naphthyl	H	H	2
p CO_2Me-C_6H_4-	p –CO_2Me	H	2
-$CH_2C_6H_5$	H	p Br	2
-CH_3	p -NHCOPh	H	3

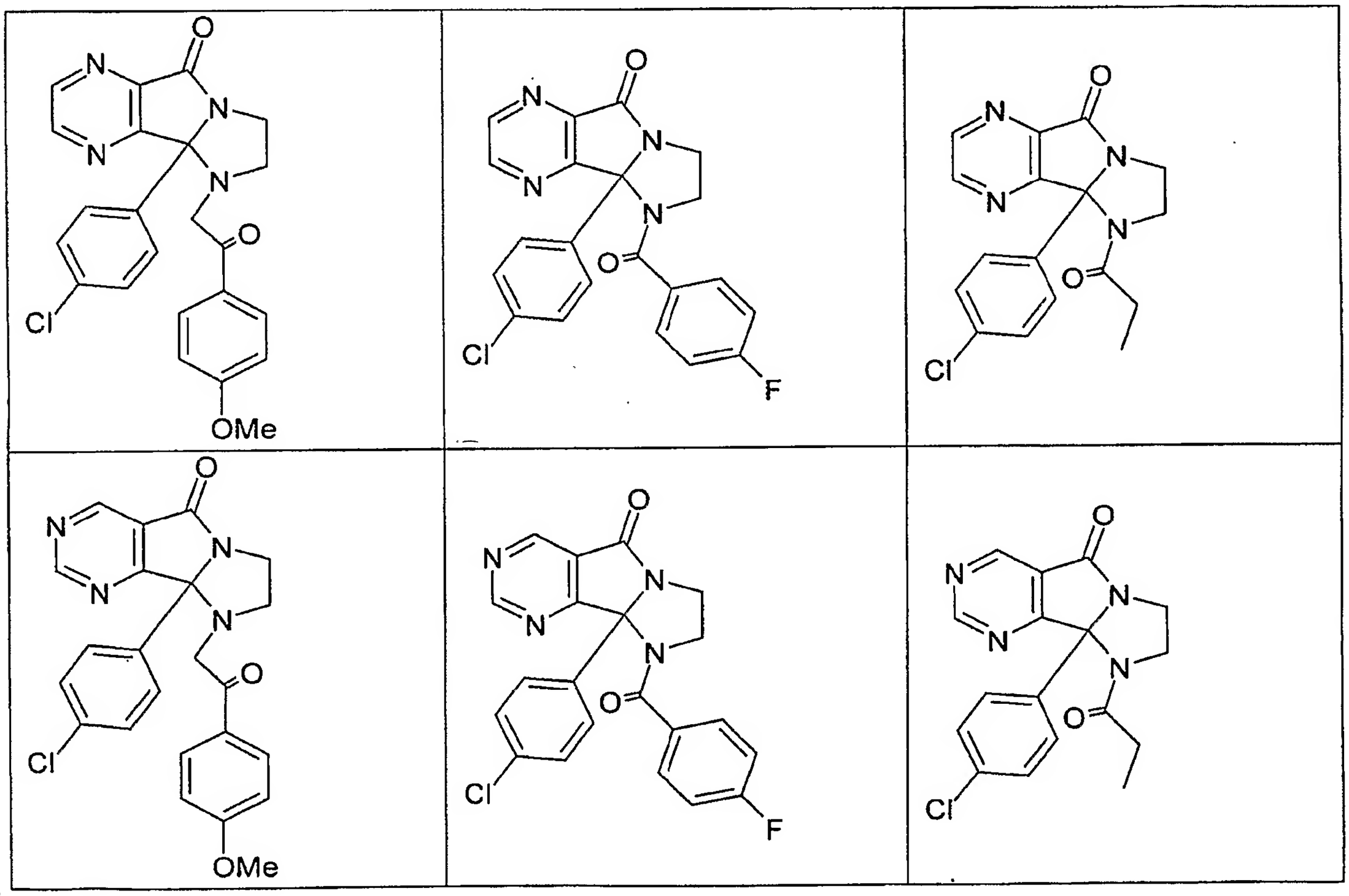
Table 4

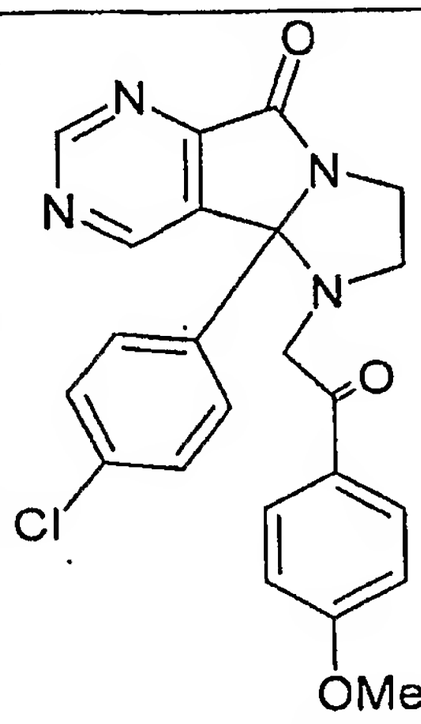
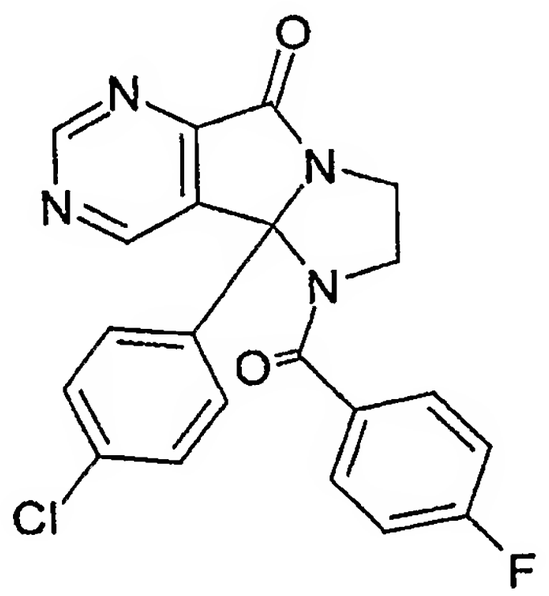
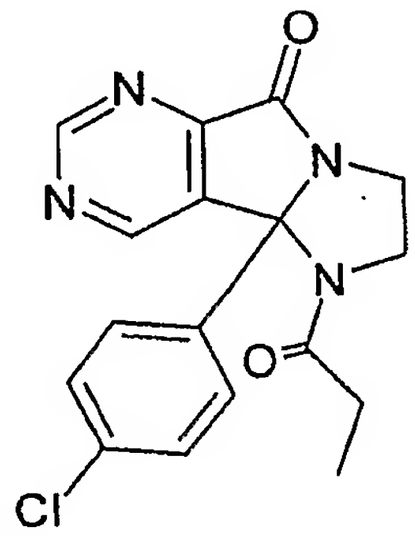
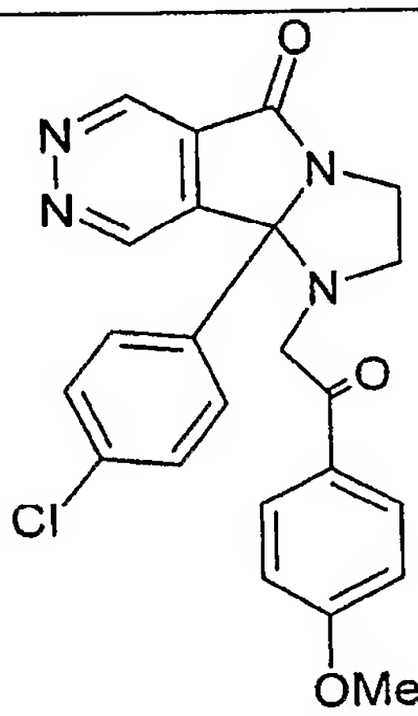
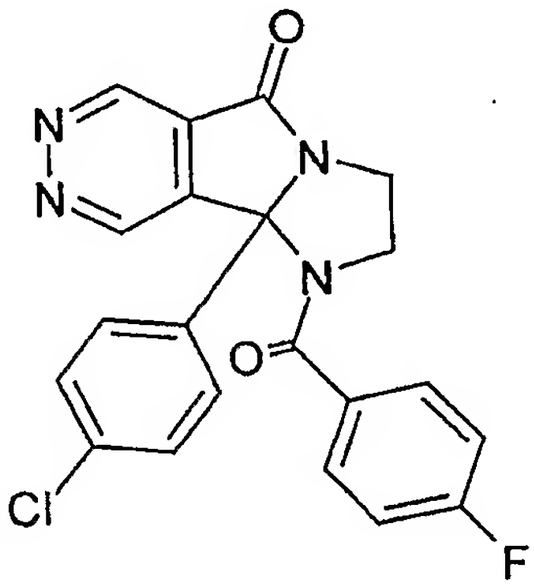
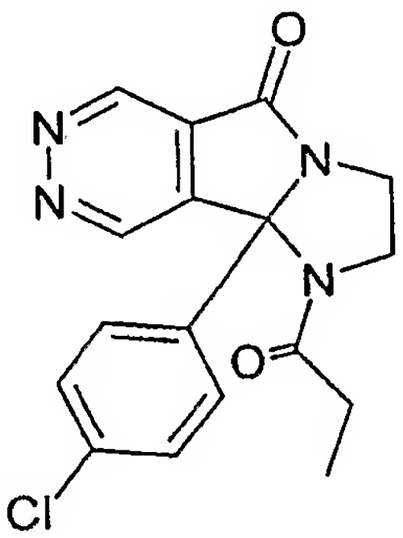
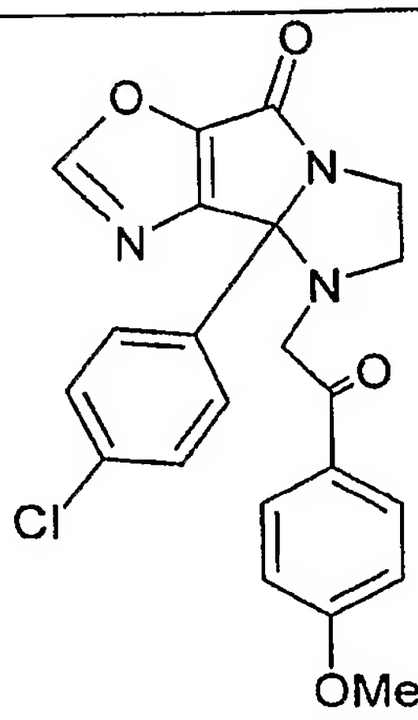
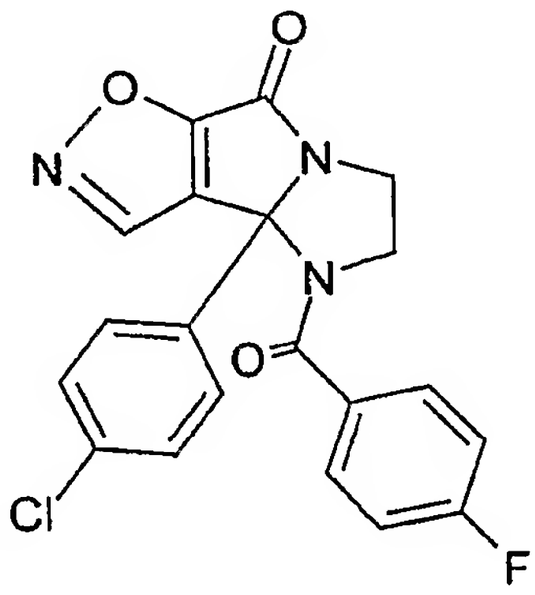
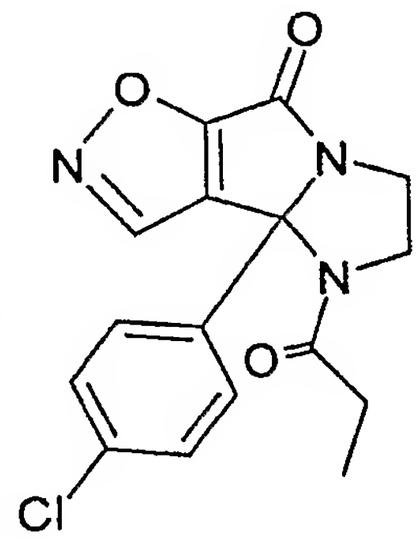


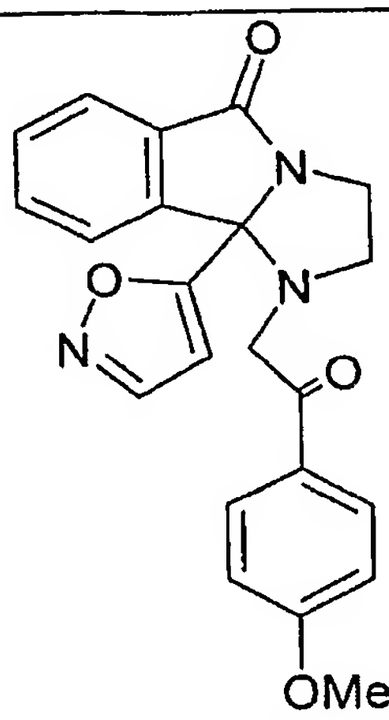
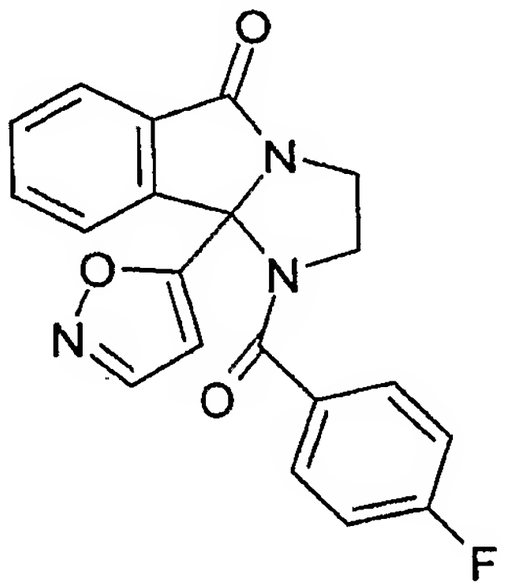
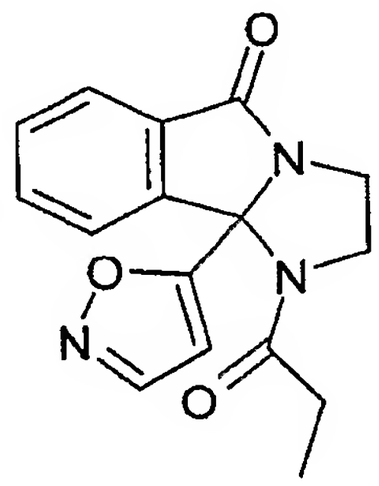
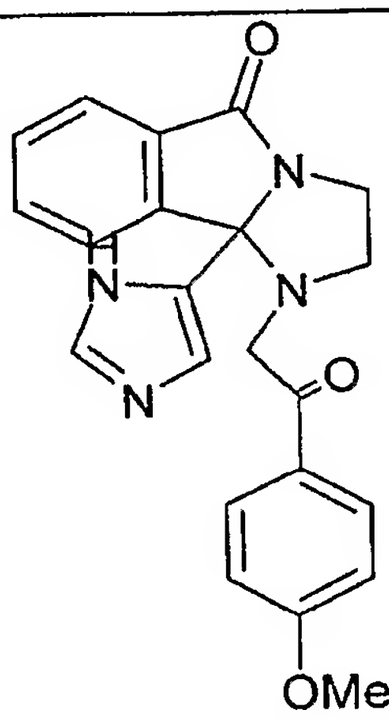
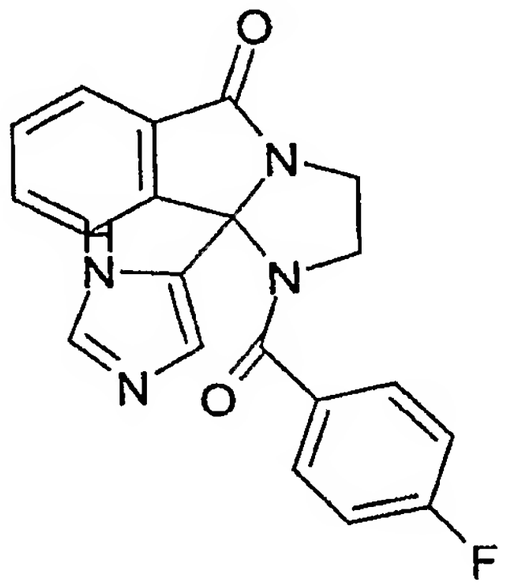
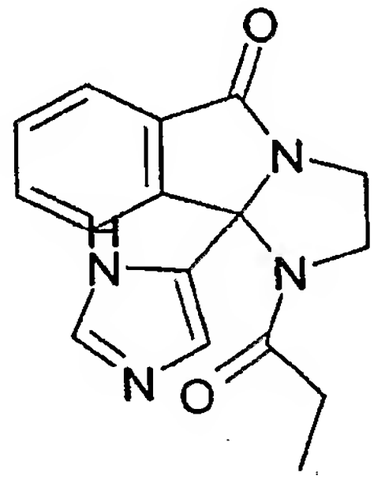
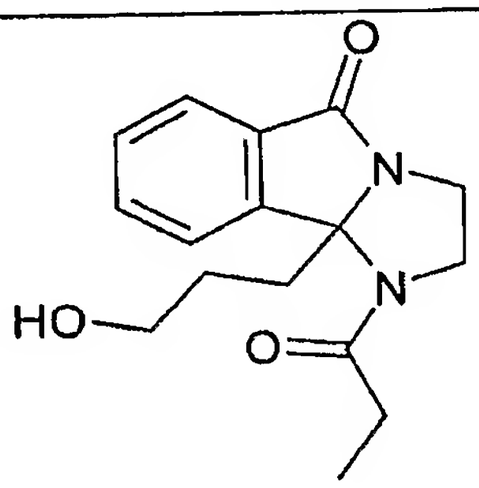
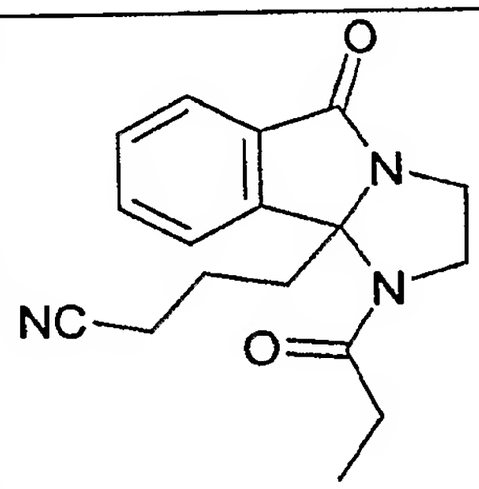
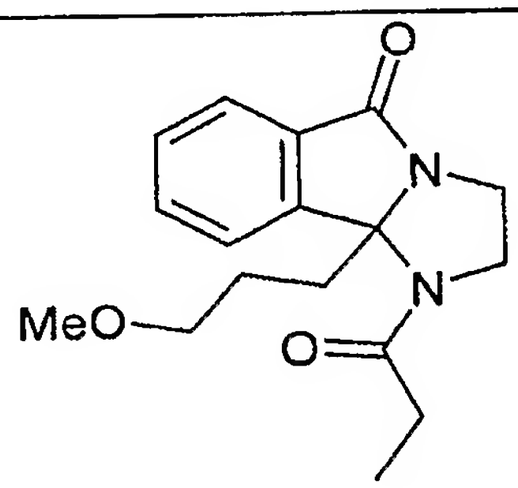
R_3	R_5	R_6	q
-CH_2NO_2	H	H	1

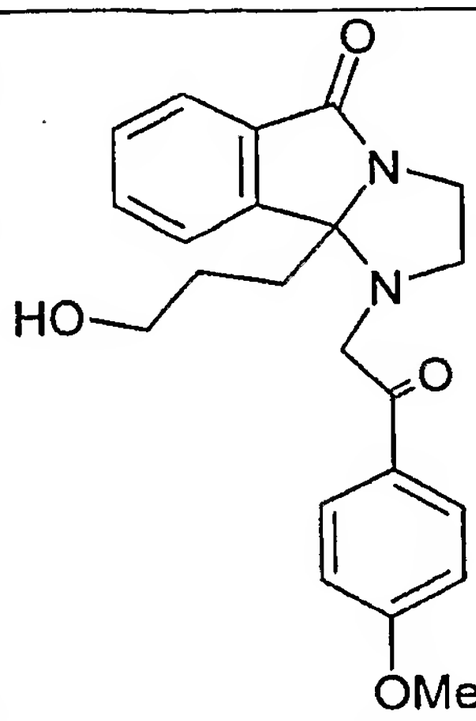
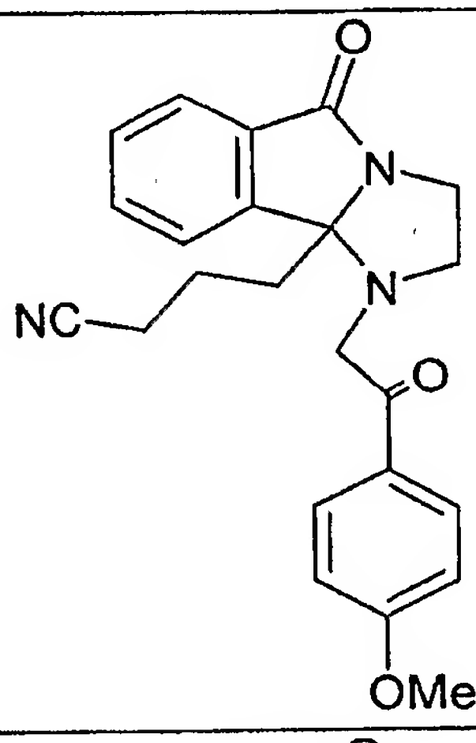
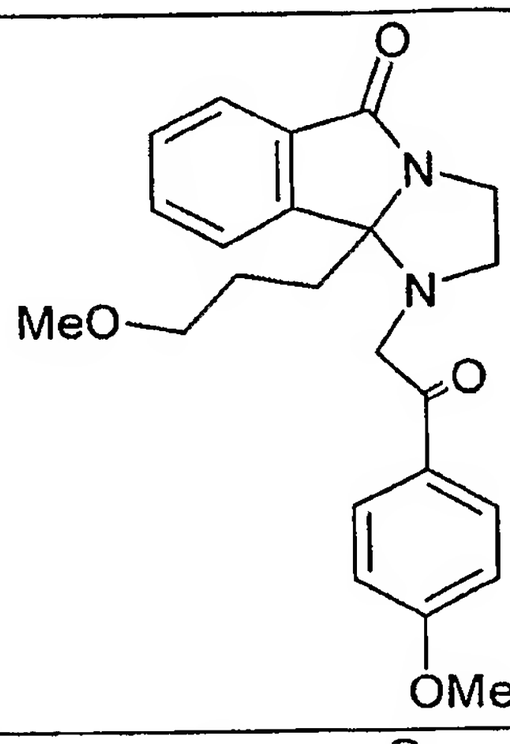
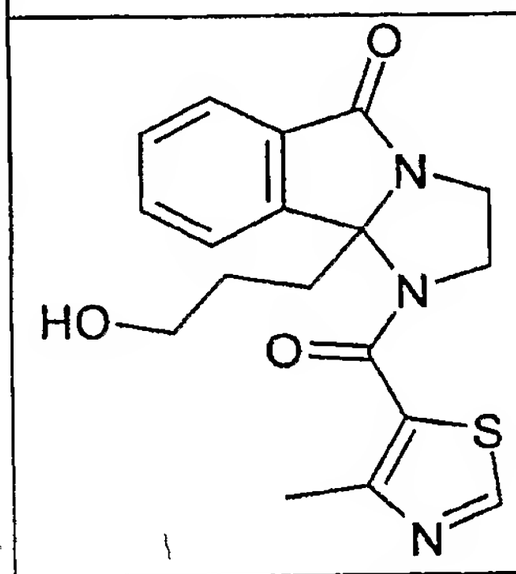
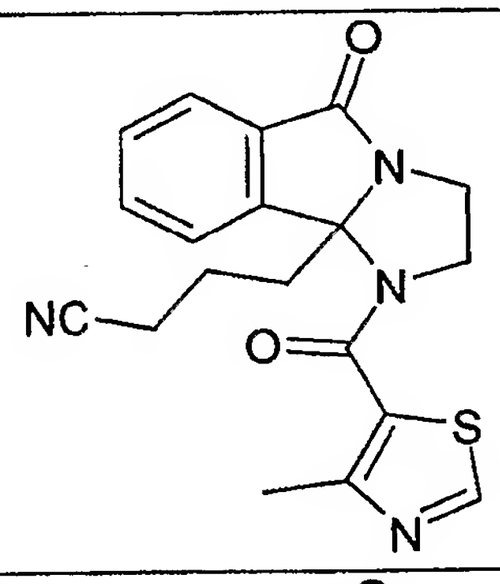
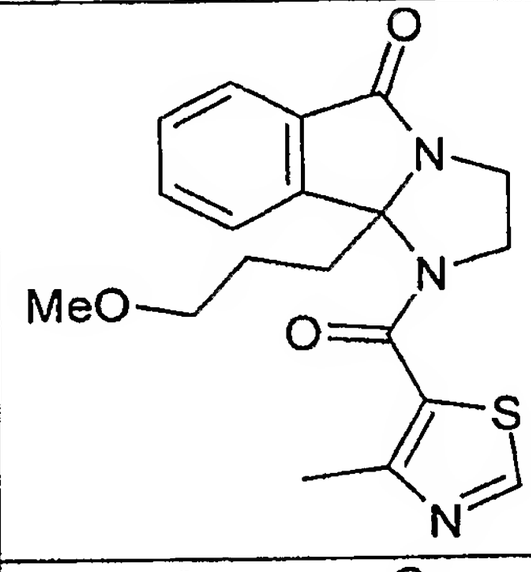
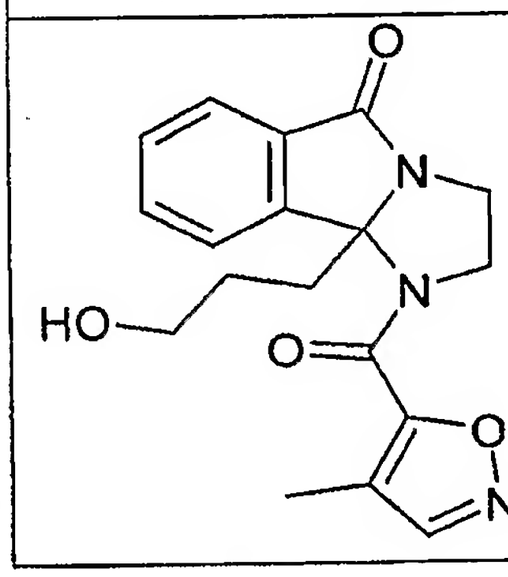
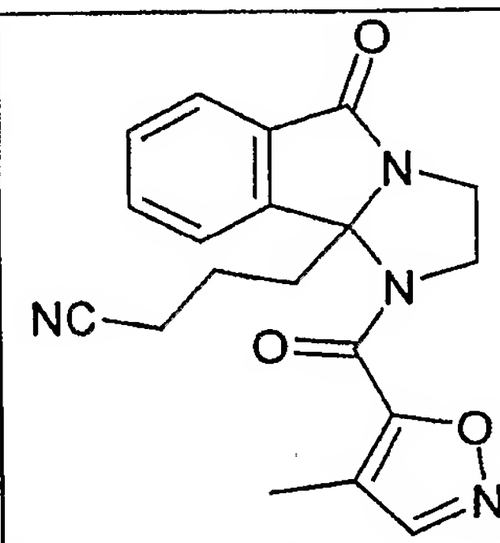
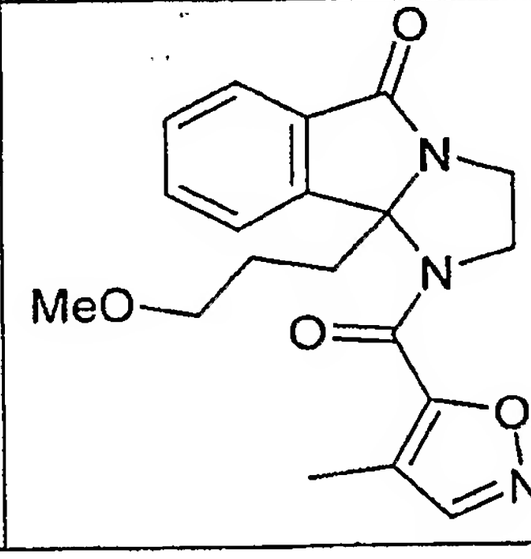
furyl	H	H	1
p $EtSO_2C_6H_4$-	o, p Cl	H	1
naphthyl	H	p Cl	2
p CO_2Me-C_6H_4-	H	p Br	2
-$CH_2C_6H_5$	H	H	3
-$(CH_2)_6CO_2Et$	H	H	3

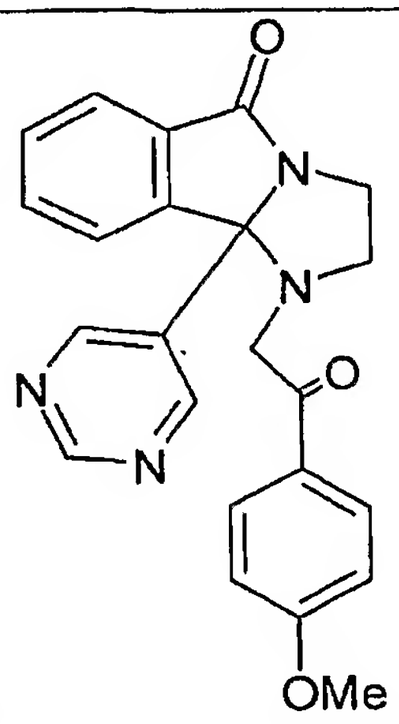
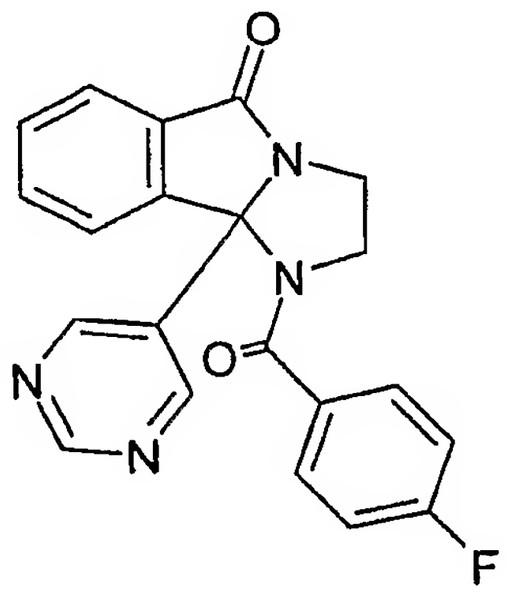
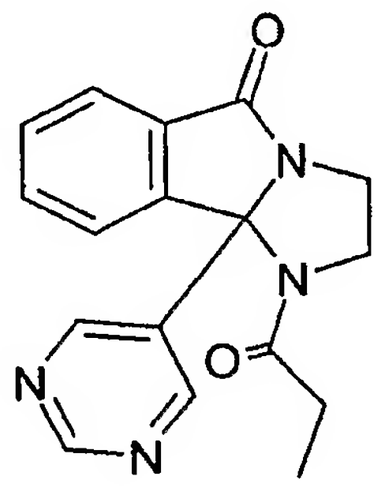
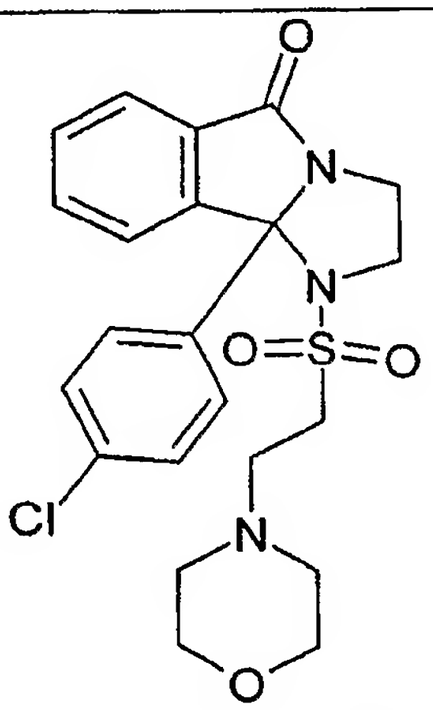
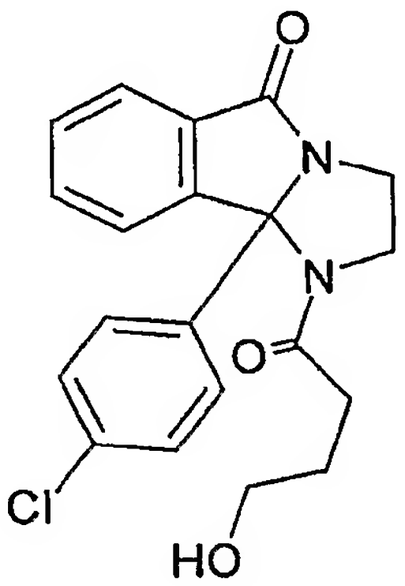
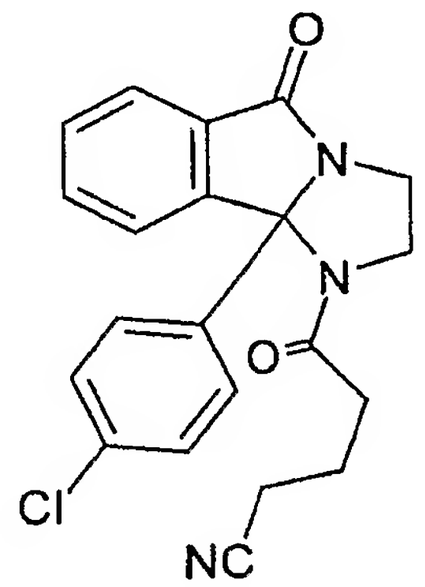
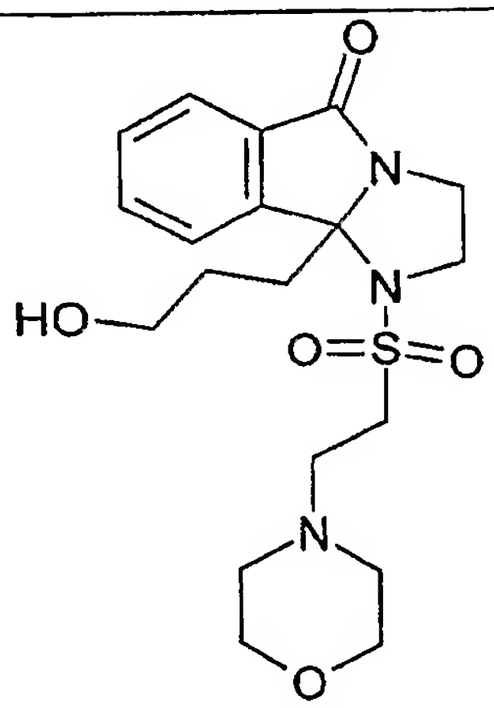
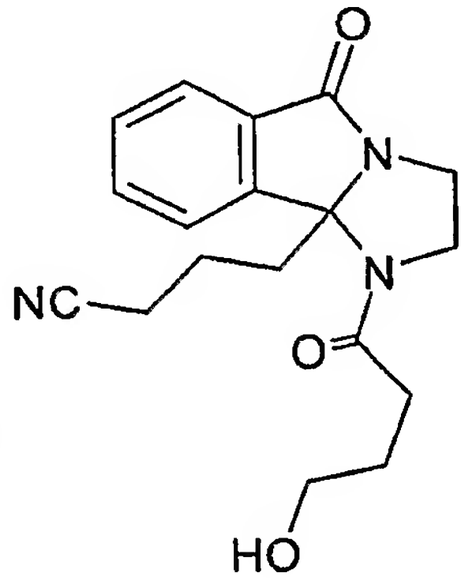
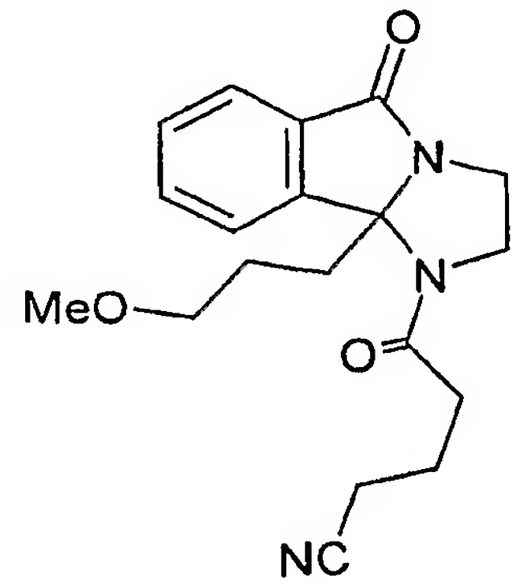
Additional compounds of the invention are depicted below.

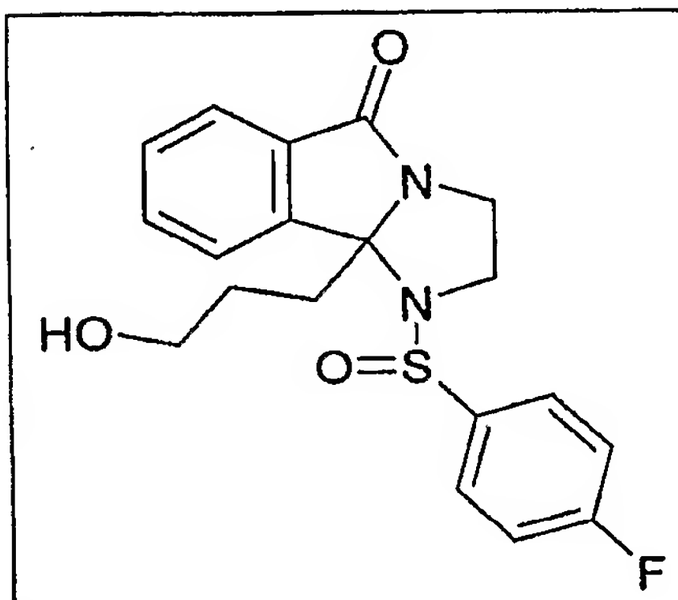
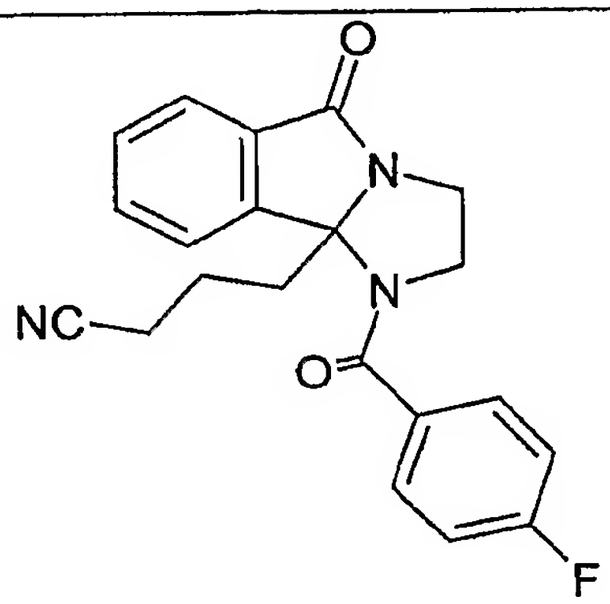
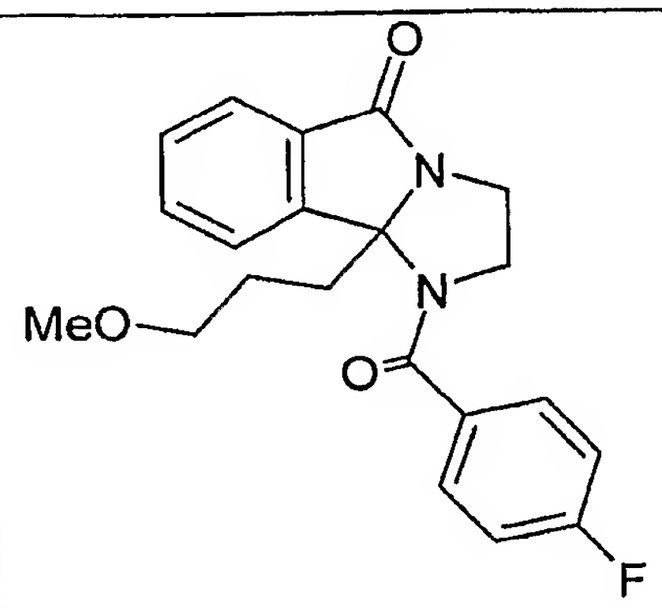
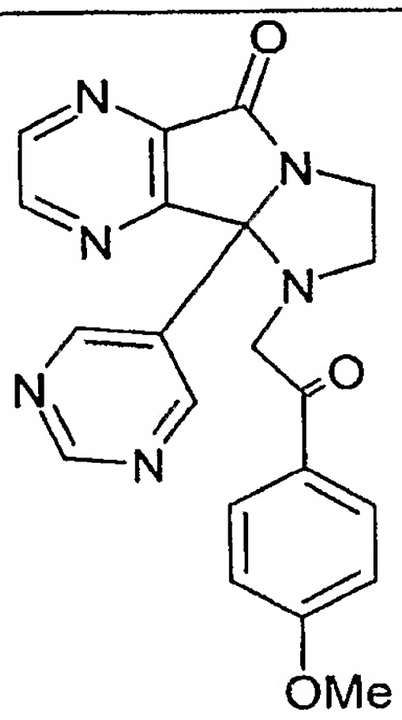
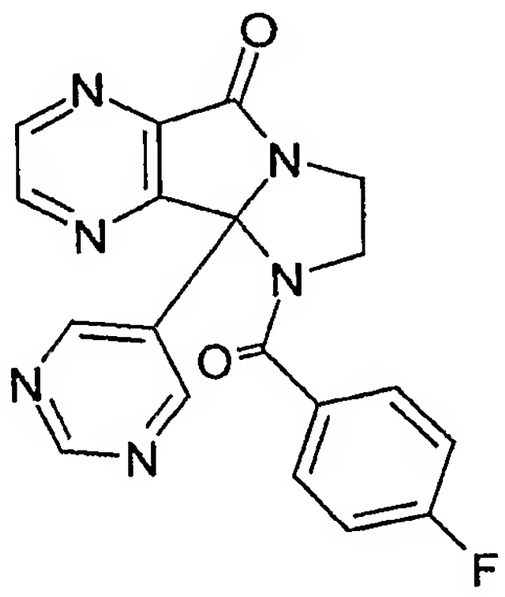
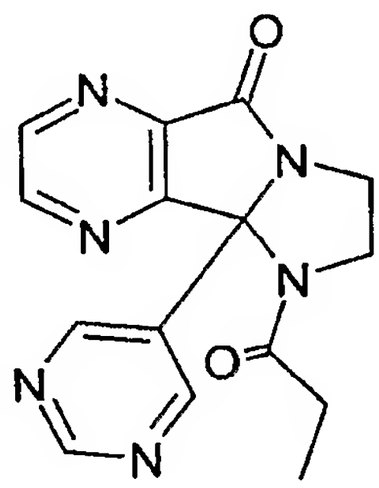
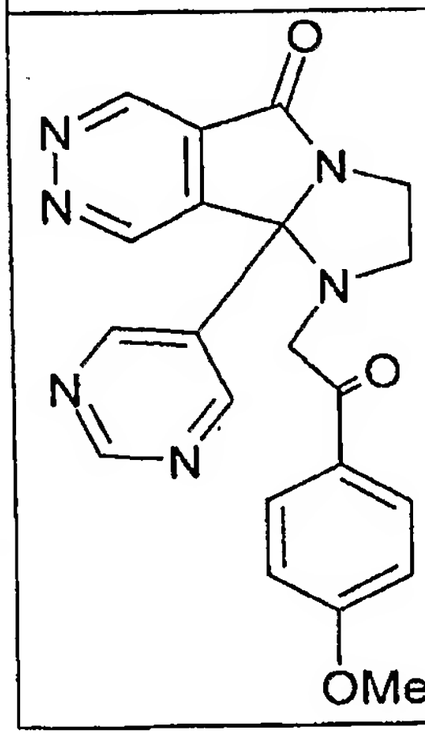
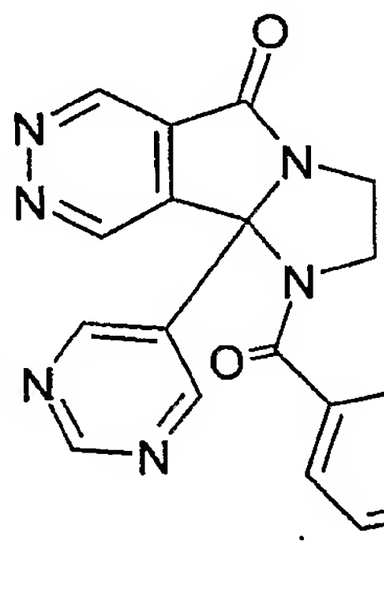
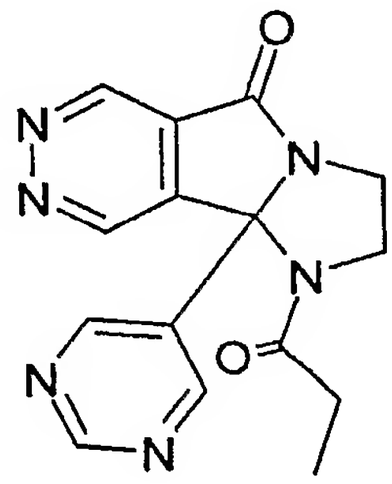


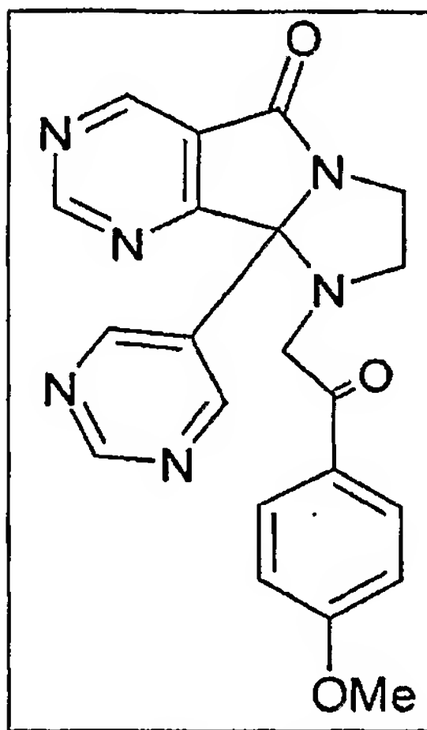
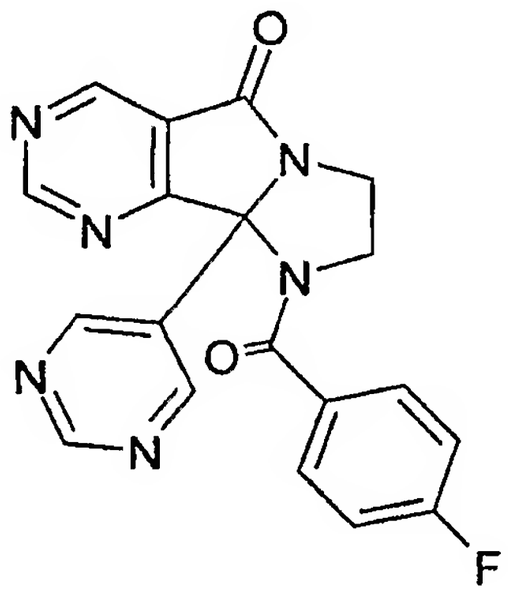
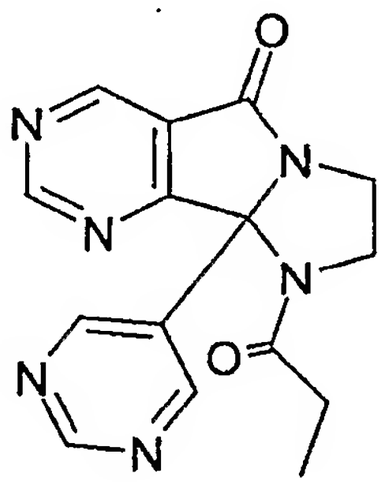
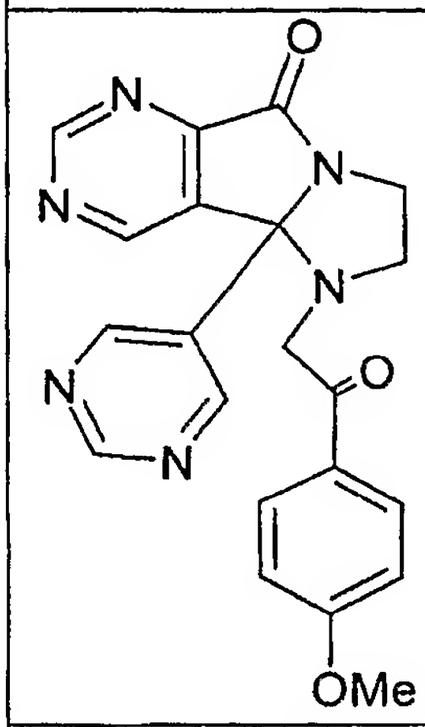
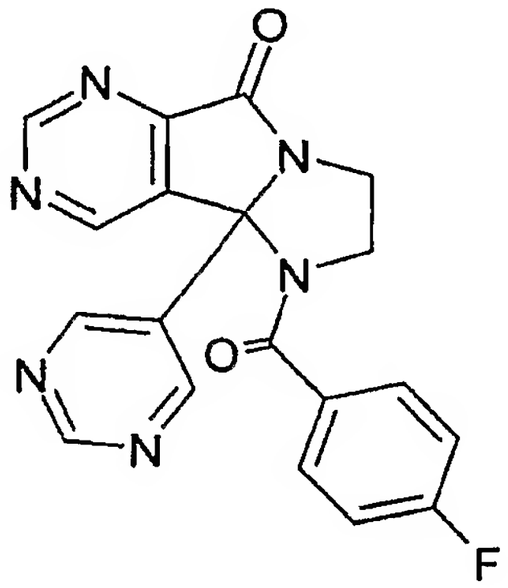
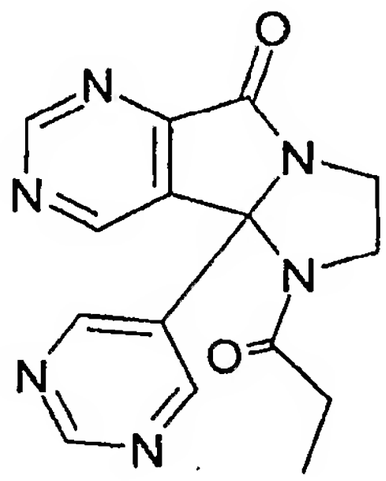
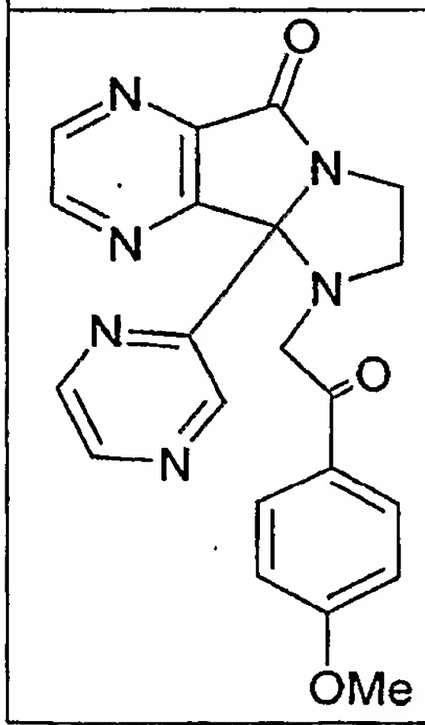
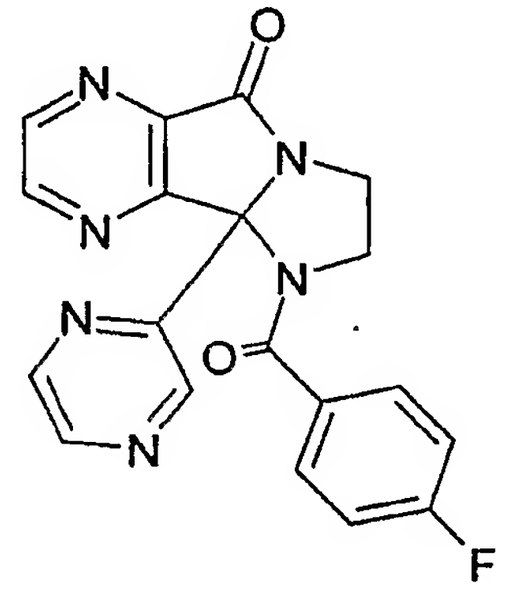
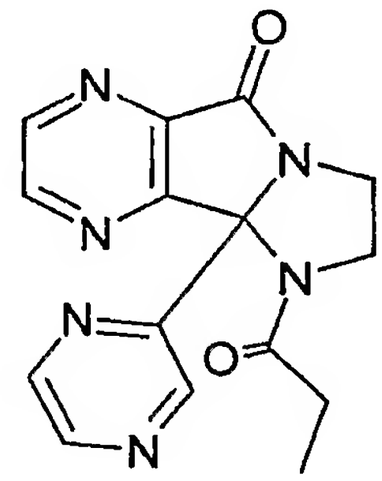
		
		
		

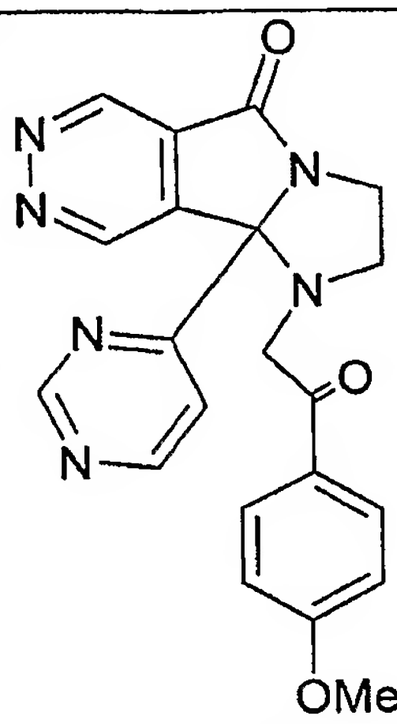
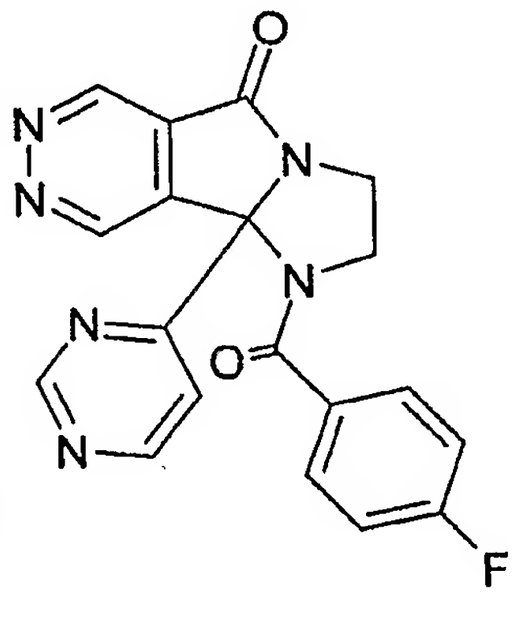
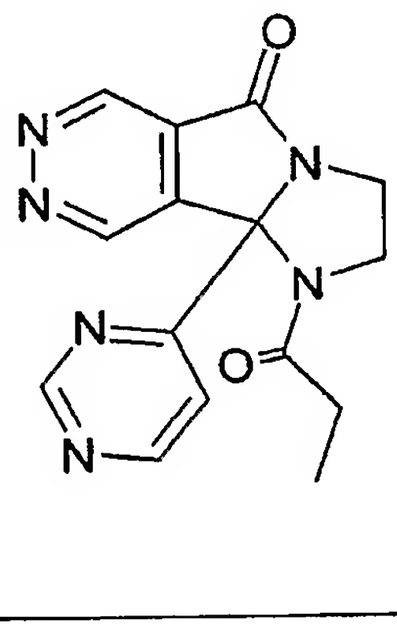
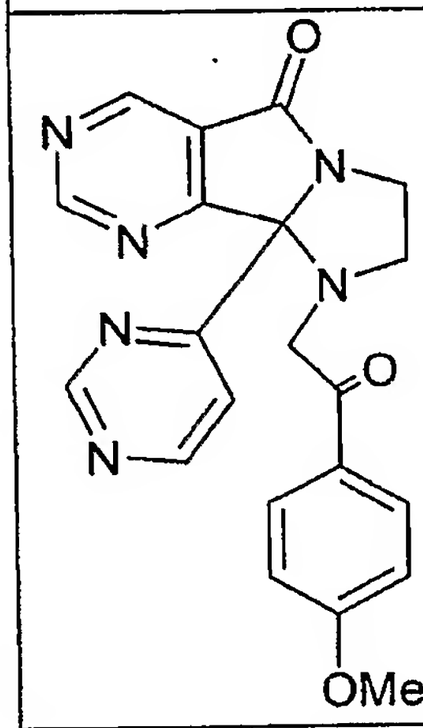
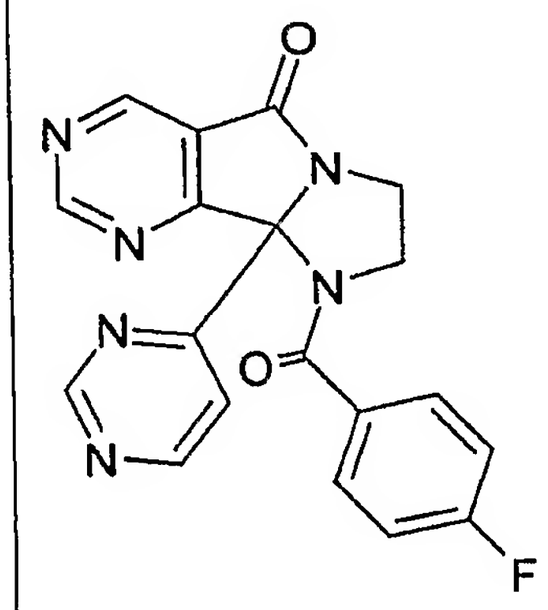
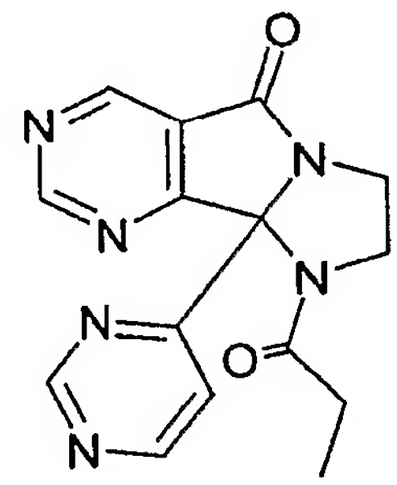
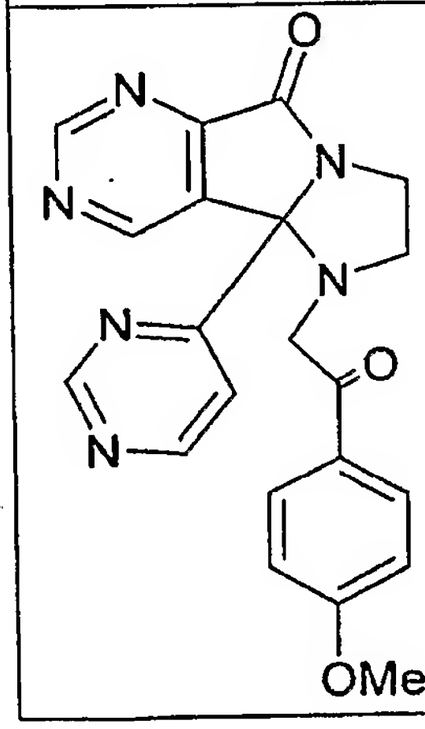
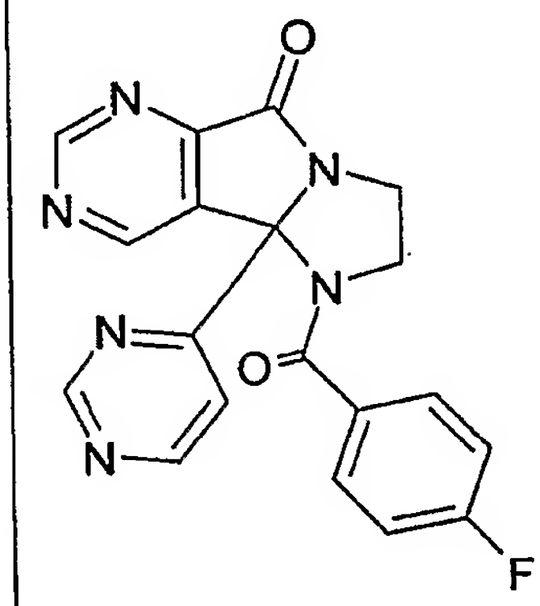
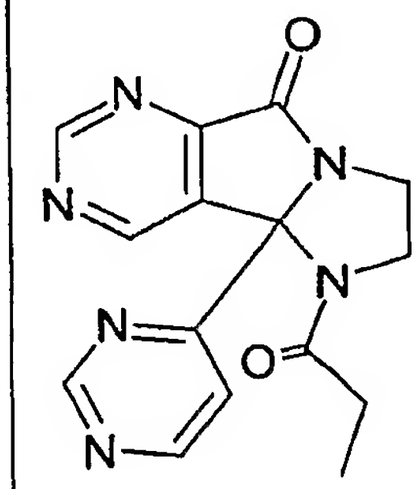
		
		
		

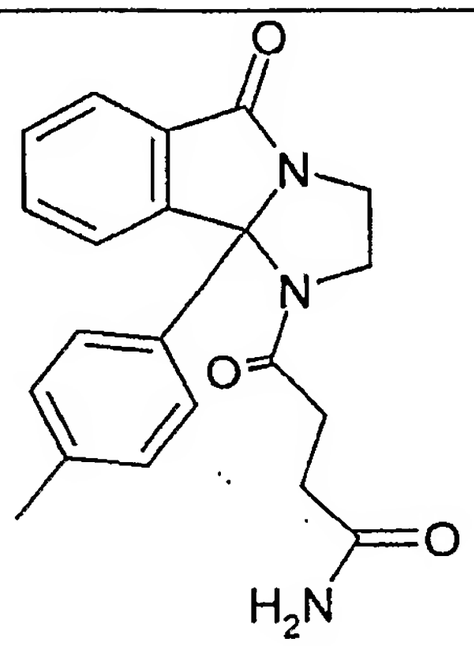
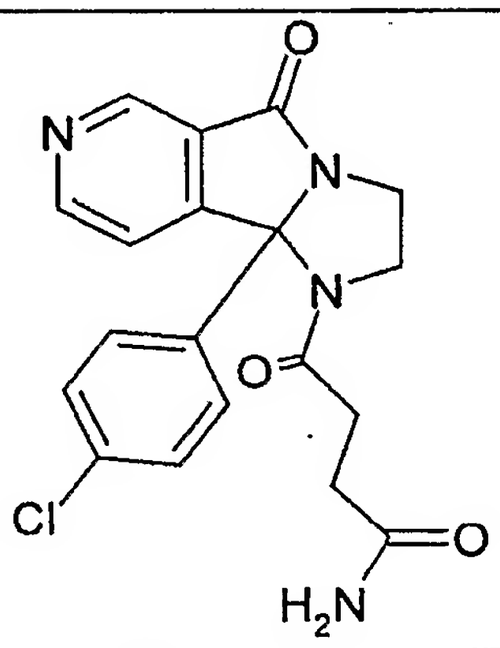
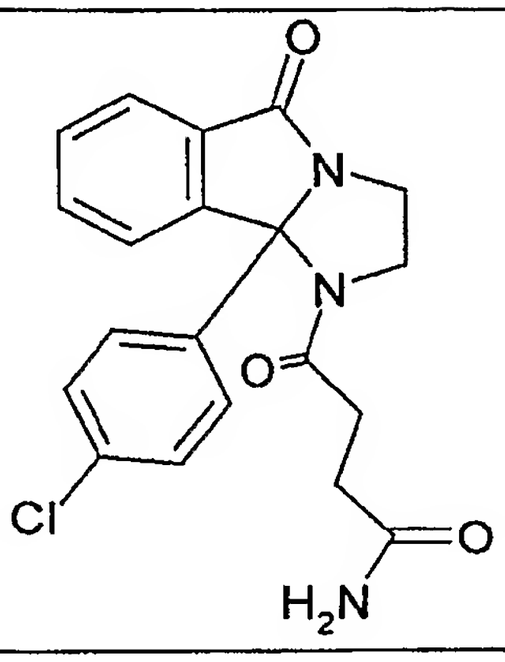
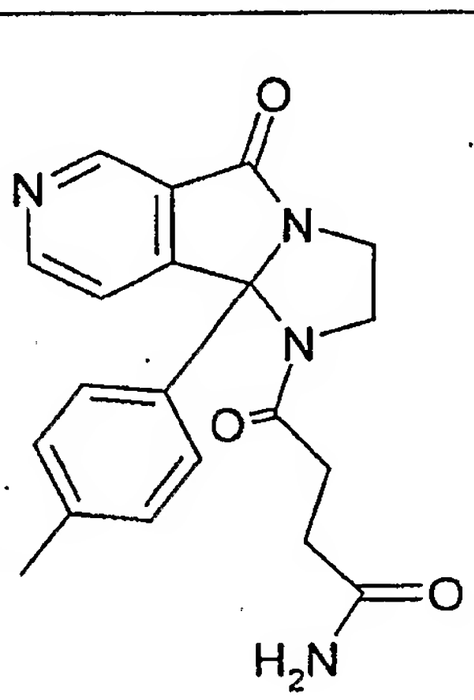
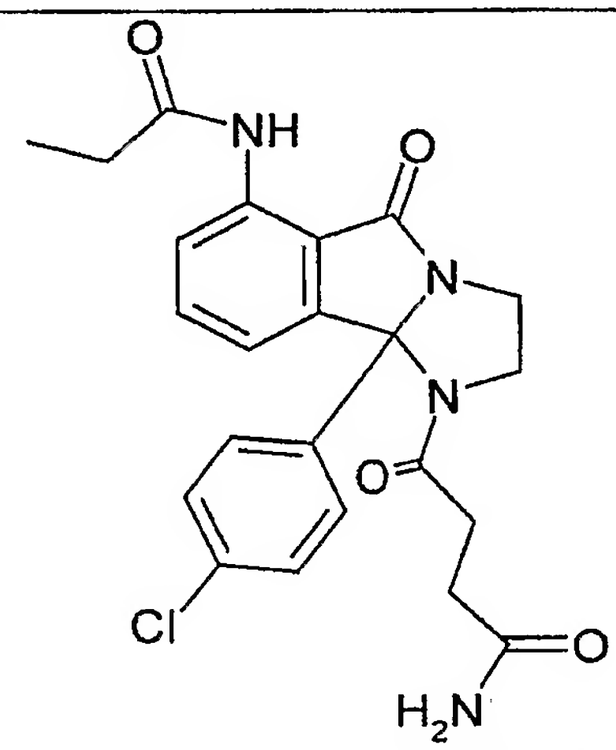
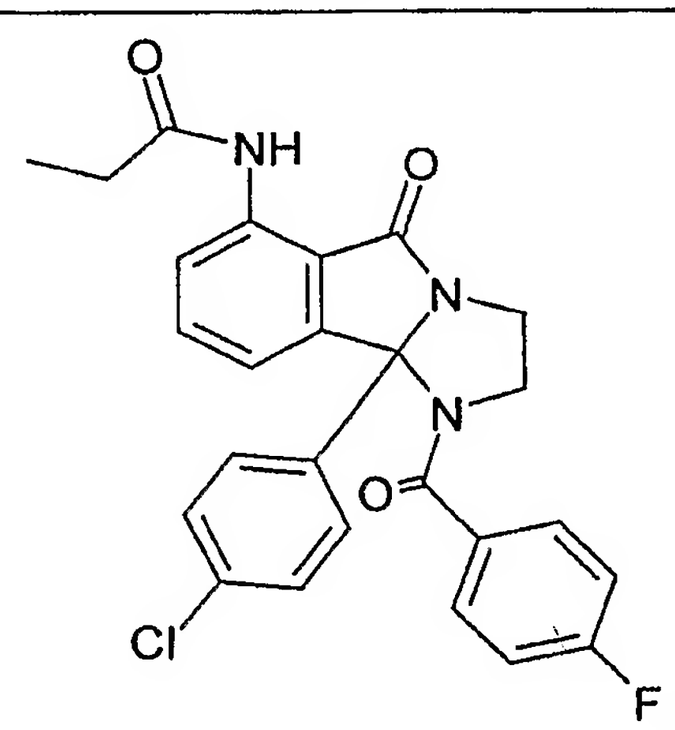
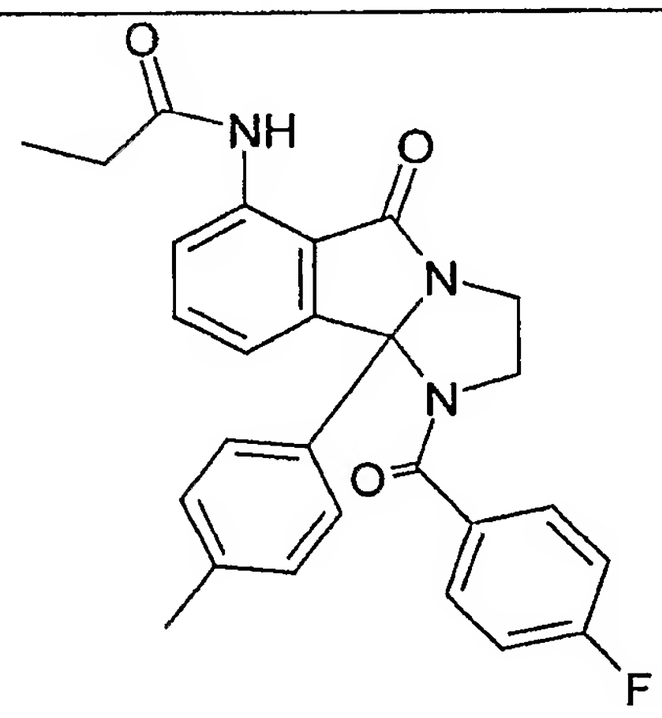
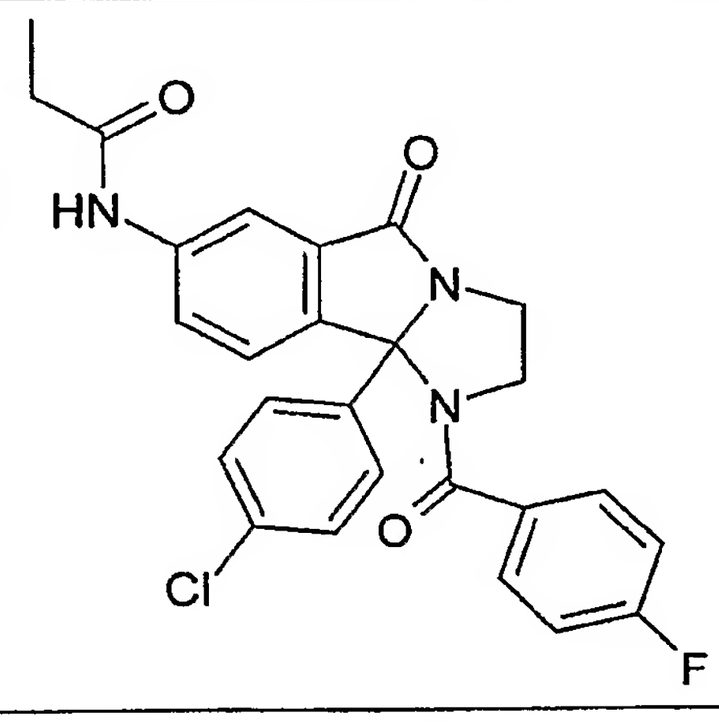
		
		
		

5

Biological Testing

The compounds of Examples 1 to 89 were tested for their ability to inhibit RSV in accordance with the methods set out in Ayisi, N.K. Gupta, S.V. and Qualtiere, L.F. (1991) Modified tetrazolium-based colorimetric method for determining activities of anti-HIV compounds J.Virol. Methods, 33: 335-344. However, for the antiviral assay, foetal bovine serum (FBS) concentrations were dropped to 2%. The examples were found to inhibit RSV with an IC50 value between 0.1μM and 50μM.

It would be appreciated by a person skilled in the art the numerous variations and/or modifications may be made to the invention as shown the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken as an acknowledgment or any form or suggestion that that prior art forms part of the common general knowledge in Australia.

DATED this 24th day of December, 2003

Biota Holdings Limited

by DAVIES COLLISON CAVE
Patent Attorneys for the Applicant